In Re)
)
Julie Baumer)

AFFIDAVIT OF JAMES A. J. (REX) FERRIS, M.D., F.R.C.Path., F.F.Path.(I)., D.M.J.

I, James A. J. (Rex) Ferris, declare as follows:

1. I am a consulting Forensic Pathologist and Professor Emeritus of Forensic Pathology at the University of British Columbia. Forensic Pathology is the branch of medicine concerned with determining the cause, manner and mechanism of a person's injury or death.

2. I am or have been registered to practice medicine in New Zealand, Manitoba, Ontario, British Columbia, Great Britain and Ireland. My educational training and degrees include an M.B., B.Ch. and B.A.O. (equivalent of American M.D.) and M.D. (by thesis) (equivalent of American Ph.D.) from Queen's University in Belfast in 1963 and 1968 respectively, a post-graduate fellowship with the Royal College of Pathologists, a post-graduate Diploma in Medical Jurisprudence from the Society of Apothecaries (London), and an honorary Fellowship in Forensic Sciences, India.

3. My previous positions include National Adviser in Forensic Pathology to the New Zealand Ministry of Justice, Head of Forensic Pathology at Hamilton General Hospital (Ontario) and Vancouver Hospital and Health Sciences Centre, and Chief Forensic Pathologist for the British Columbia Coroners Service. In addition I have held various academic positions and fellowships including Professor of Forensic Pathology at the University of British Columbia from 1983-1999. In these capacities, I have researched and published in the areas of sudden infant death syndrome, mechanisms of head injury in infants and children, and "shaken baby syndrome." I have consulted on over 80 pediatric forensic cases for the prosecution and defense. My curriculum vitae is attached as Ex. A.

4. Since pediatric head injury (brain damage) can be natural, accidental or non-accidental in nature, a determination of causation requires a thorough review of the child's medical records and clinical history, starting with prenatal records and family history and continuing through imaging and, if applicable, autopsy slides.

5. I have been asked to review the medical records for Philipp Baumer and have done so on a *pro bono* basis. My review included the following records, which are of the type ordinarily relied upon in forming opinions on the nature and cause of pediatric head injury:
   - emergency department records from Mt. Clemens Hospital dated October 3, 2003, including laboratory reports;

- hospital records from Children's Hospital of Michigan beginning October 3, 2003, including CT scans and MRIs;
- transcripts of testimony presented at Julie Baumer's trial;
- prenatal, neonatal and pediatric records;
- a birth video (with transcript); and
- various interview reports.

6. I do not have the labor and delivery records (other than a one page synopsis) or the laboratory reports from Childrens Hospital, and I understand that these are not currently available.

7. Based on my review of the available documents, I have formed an opinion on the nature, cause and timing of Philipp Baumer's medical condition, which I hold to a reasonable degree of medical certainty.

8. The medical records are inconsistent with blunt force trauma or abuse occurring shortly before hospital admission. The skull fracture shown on the imaging is not accompanied by either the tissue swelling or hemorrhage that would be expected in association with a very recent fracture, and there were no external or internal bruises. In my experience, a skull fracture of this size would produce bruising that would take at least 7-10 days to resolve. The fracture is consistent with birth injury or with a minor fall. In this case, the medical records indicate it is more likely the result of birth injury.

9. The imaging and medical records indicate that the child's collapse on October 3 was due to obstruction (clotting) of the arteries or veins, most likely the veins, rather than trauma. Venous sinus thrombosis (clotting of the veins that drain the brain) accounts for approximately 30% of childhood stroke and is commonly associated with dehydration, infection and/or illness in infants under the age of 3 months. Given the extent of the infarcts (dead tissue) in the areas of vascular distribution of the veins, it is likely that the thrombosis occurred within 24-72 hours of the first CT scan, *i.e.*, shortly before hospital admission or during hospitalization. The clinical history and medical records suggest that the child may have begun to thrombose the night before hospitalization, or that the child's illness may have triggered later thrombosis, possibly in conjunction with the seizures observed in the hospital. It is not possible to determine the precise sequence of events since no head imaging was done until nearly a day and a half after the child's hospital admission.

10. Viewed as a whole, the records present a classic pattern of venous sinus thrombosis, most likely caused by some combination of birth injury, infection, illness and dehydration. This pattern is described in two articles in the New England Journal of Medicine, one of the most prestigious American medical journals (Atts. B and C). Articles in the specialty journals are in accord.

11. In this affidavit, I identify some of the key findings in the medical records and

trial testimony.

12. Prenatal records. The records indicate that Philipp's mother was drug addicted (polysubstance abuse, including crack cocaine). She was treated for dehydration on 1/7/03 and tested positive for marijuana on 1/31/03. Subsequent drug tests were negative. She reported one prior seizure (6/02). A pap smear showed inflammation on 2/13, and trichomoniasis was diagnosed on 3/5. Trichomoniasis is a parasitic sexually transmitted disease associated with adverse effects in pregnancy, including cerebral palsy. On 3/28, the mother almost passed out at work, with ambulance response. Tests conducted during pregnancy indicated low hemoglobin, hematocrit and lymphocytes; high neutrophils (suggesting infection); and somewhat abnormal blood sugar. The mother went to the hospital on 7/16 (vomiting, diarrhea), 8/2 (ill, vaginal discharge, mild dehydration), 8/8 (contractions 3 times a day, 3 minutes apart), and 8/16 (flu-like symptoms). The mother had earlier reported contractions (7/21). The child was induced on 8/16 at 38 weeks (two weeks before the due date). The family history includes diabetes and death of the mother's twin from congenital heart disease shortly after birth.

13. Labor and delivery. I do not have the labor and delivery records, but a one page summary indicates that Philipp was induced with oxytocin, a drug used to start or augment contractions. Since the child was not large and there are no recorded signs of maternal or fetal distress, the reasons for induction are unclear. Oxytocin requires careful monitoring of the mother and fetus and has a small but well-recognized risk of brain damage and/or death in infants.

14. The records indicate that labor was induced around 3 a.m. but that full dilation did not occur until approximately 5:40 p.m. According to the family, a C-section was considered when the mother had not dilated after approximately 12 hours of labor and the child appeared to be in the birth canal, without progress. Since the labor was extended and had unusual features, the labor and delivery records should be carefully reviewed for specific information on dilation, medications and the reason(s) for induction.

15. A birth video of the last five minutes or so of labor shows a natural vaginal birth, with episiotomy but without forceps or ventrouse extraction. The child was 6 lbs 8 oz and 19" at birth, with apgars of 8 (normal). A hospital chart indicates that, based on development, he was likely born at 37 rather than 38 weeks.

16. A transcript of the remainder of the birth video indicates that the child was discolored after birth, suggesting lack of oxygen. The child's face was bruised and he had a cut on its forehead, suggesting birth trauma of some type. Other reports indicate that the child's face was swollen and his right side limp.

17. Neonatal records. Philipp was placed in a special care neonatal ward for one week due to vomiting and failure to suck. During this period, he was given antibiotics and fed largely by gavage (tube feeding). Lab reports indicate high neutrophils (possible infection), erratic glucose (blood sugar), low calcium, and

jaundice. The nursing notes confirm the facial bruising. On 8/19, the child had brachycardia (slow heart rate) and critically low glucose (blood sugar). It does not appear that head x-rays, CT scans or MRIs were taken. Combination bottle and gavage feeding continued until discharge on the morning of 8/23. His discharge weight was 6 lbs 6 oz. (8/18 height recorded as 20.9"). No special feeding instructions were given.

18. Pediatric records. Philipp was seen by a pediatrician on 8/26, at which time he had regained his birthweight of 6 lbs 8 oz. and had a recorded height of 20". The pediatrician recommended a one month recheck. On 8/29, Philipp was brought in for six episodes of leg and tongue twitching and tremors. His recorded weight was 7 lbs. Philipp had a one month well baby visit on 9/23, at which time his weight was recorded as 8 lbs 10 oz. and height as 21.5". An October 3 pediatric note indicates that he was referred to the E.R. because he had a poor appetite, refused to eat and was very fussy.

19. Caretaker reports. At trial, the grandmother testified that from hospital discharge through September 28, Philipp slept too much, had a limp right arm and poor sucking reflex, and ate poorly. She described a period of rapid blinking on September 27. The grandfather testified that, 25 minutes after birth, the child had a blue mark or bruise on the side of his face, extending almost to the jawbone; a bleeding or bloody laceration by the hairline; and abnormal color, causing the grandfather to wonder whether he was bi-racial. After discharge, the grandfather reported that the child was inactive, often vomited, had a weak cry and ate poorly.

20. In subsequent interviews, the grandparents confirmed the bruising and laceration and described Philipp as a hard-to-feed baby, with a limp right side, who slept most of the time but was fussy when awake, with episodic twitching and eyeblinking. They did not think he grew much after hospital discharge. The grandfather was concerned that he showed no reaction to a hand waved in front of his face, and the grandmother reported an unusual cry the night of October 2. A colleague in Kiwanis reported that Julie said she had to feed him in "thimblefuls" and that Philipp did not eat or interact during the 4-5 hours that she cared for him.

21. Mt. Clemens records. Philipp was admitted to the emergency department at Mt. Clemens General Hospital at 1:05 pm on October 3, 2003. The caretaker reported that he had episodes of emesis (vomiting) the prior night and had not eaten since. He was floppy, lethargic and not acting normally, and Dr. Olson's office advised taking him directly to the emergency room. A physical examination confirmed that he was floppy, dehydrated and ill appearing, with eyes deviating to the right. Examination revealed no bruising, unusual marks, or external signs of injury. His recorded weight was 6 lbs. During a neonatal consult, Philipp became apneic (temporarily ceased breathing) and had a seizure. His EEG suggested seizure activity, and his laboratory tests showed high white blood cells and neutrophils (indicating infection); critically low hemoglobin and hematocrit (anemia) and blood sugar (hypoglycemia); critically high BUN and potassium (renal failure); and a positive bacterial culture.

22. The attending physician, Dr. Mok, diagnosed severe dehydration, sepsis, acute renal failure secondary to dehydration, anemia, hyperkalemia (increased potassium levels), hypoglycemia, apnea, positive gastro-occult, and possible intracranial hemorrhage. The child was rehydrated, given IV antibiotics and stabilized. Given the possibilities of hemolytic uremic syndrome (HUS) or severe sepsis (infection that has spread to the bloodstream), he was transferred to a pediatric ICU at Childrens Hospital. No CT scan was performed at Mt. Clemens per request by Childrens.

23. Childrens Hospital. Philipp was admitted to Childrens at 5:40 p.m. on October 3. Admission records indicate that he weighed 7 lbs 4 oz (3284 g) and was 21.85" (55.5 cm) on admission. A summary report indicated that he had a 24 hour history of vomiting and appeared very dehydrated; that there were no external signs of abuse; that the eyes deviated to the right; and that the mother reported that he was floppy and unresponsive today. The note indicates a recent weight of 8 lbs 10 oz (last week) and 6 lbs as of 10/3. The initial diagnoses were septic shock, with seizure and hypertension. Lab tests (including coagulation) were ordered, but the results are not contained in the records provided. Blood transfusion was approved, presumably to correct anemia.

24. An ultrasound of the head was taken at 8:01 a.m. the following morning, approximately 19 hours after hospital admission. The report indicated abnormal brain parenchyma on the right side. Possibilities included ischemia (lack of oxygen to the brain), possibly from hemorrhage or inflammation. A followup CT scan or MRI was recommended for more detailed evaluation. An EEG showed frequent epileptic seizures.

25. At 7:30 pm, the medical staff requested a neurosurgery consult as the child's fontanelles had become tense and possibly bulging, indicating increased intracranial pressure and brain swelling.

26. The first CT scan was taken at 9:39 p.m., approximately 32-33 hours after initial hospital admission. The radiology report indicates parenchymal hemorrhage with obscuration of gray-white matter interface, infarcts (dead or damaged brain cells), and a right parietal diastatic fracture. Although the radiologist indicated that "the constellation of the above findings is highly suggestive of non-accidental trauma," such diffuse findings are not diagnostic of trauma (which would more likely show large localized hemorrhage) but suggest a reduction in blood flow, venous obstruction and associated patchy venous infarction, *i.e.*, childhood stroke. The absence of subscalpular and external bruising indicates that the fracture is much older, at least 10-14 days before the first CT scan and possibly present from birth.

27. A neurosurgery note at approximately 11 pm indicated a preoperative diagnosis of ischemia (lack of oxygen to the brain) and cerebral edema (an accumulation of fluid around the brain cells). A shunt was inserted to reduce intracranial pressure. Antibiotics were continued and the child was given heparin, an anticoagulant that decreases clotting but increases the tendency to bleed.

28. On October 5, an ophthalmology consult indicated diffuse vitreous and intraretinal hemorrhage. An October 6 skull x-ray confirmed that the sutures (normal gaps in the unfused infant skull) and fracture were widely separated, presumably from brain swelling and increased intracranial pressure. An October 6 bone survey found no rib or other fractures apart from the right parietal fracture.

29. An October 9 CT scan was similar to the October 4 scan, with only minor improvements. An October 10 EEG indicated increased risk of epileptic seizures. An October 16 ultrasound of the eye showed right retinal detachment with associated hemorrhage. An October 20 chest x-ray confirmed that there were no acute or healing rib fractures. An October 30 MRI identified "several foci of acute blood," indicating an ongoing process within the brain, most likely related to compromise of blood supply caused by obstruction of the veins or arteries.

30. A December 17, 2003 letter from Dr. Cristie Becker, a pediatric radiologist, to Detective Sergeant Rollo of the Macomb County Sheriff's Department states that the October 4 CT scan is most consistent with an injury of at least 12 hours and most likely within 48 hours. Dr. Becker attributed the skull fracture to the skull striking a larger flat surface but confirmed that this could not cause the severe brain injury, which she said is "much more typical of repetitive injury such as that seen in intentional, violent shaking of the child." Dr. Becker attributed continued hemorrhaging in the October 9 CT scan to resuscitation and supportive therapy. Since the brain injuries in the 10/30 MRI scan seemed to be evolving at a similar rate, she concluded that the brain injuries (but not the fracture) appear to have occurred at or near the same time and recommended a careful review of the obstetrical records to exclude a forceps delivery as the cause of the fracture. She indicated that a small amount of swelling in the area of the scalp near the fracture suggested a 2-3 day old injury rather than a birth injury.

31. An August 12, 2004 radiology report indicated that the pattern of brain damage suggested "the possibility of an ischaemic event," *i.e.*, lack of oxygen to the brain.

32. Trial testimony. The trial testimony of the State's witnesses on the cause and nature of Philipp's brain damage was inconsistent. Much of the confusion arose from the failure to recognize that the diffuse nature of the brain damage seen in the October CT scans and MRI suggests natural causes, specifically, obstruction of the veins, rather than trauma.

33. Dr. Mok, the emergency room physician, repeated his earlier diagnoses of severe dehydration; sepsis; renal (kidney) failure secondary to dehydration; anemia with hemolysis (broken blood cells); hypoglycemia (low blood sugar); apnea (cessation of breathing, addressed with resuscitation and life support); positive gastro-occult; and possible intracranial hemorrhage. He testified that there was no evidence of head wounds, that dehydration can occur very quickly in a child, and that Philipp's symptoms could be caused by many factors, including illness, injury, kidney failure, liver disease, brain injury or hereditary issues. He testified that signs of child abuse included bruising or broken arms without explanation or

inconsistent history, or with a pattern of repetitiveness.

34. Dr. Ham, the neurosurgeon, testified that the CT scans showed a skull fracture and bleeding and other changes in the brain that indicated ischemia or decreased blood supply. He testified that he inserted a shunt to remove fluid and relieve the intracranial pressure. Dr. Ham testified that the brain injury occurred within 12-24 hours of the CT scan, which was taken 32-33 hours after hospital admission, placing it well within the period that the child was in the hospital. Dr. Ham testified that the skull fracture could be accidental and could have occurred from "surprisingly little" force, such as a fall from a changing table or being dropped two to three feet. In his view, the brain damage was not consistent with a fall and was caused by significant blunt force and an "intentional act." He also testified (incorrectly) that retinal hemorrhages are virtually pathognomonic of nonaccidental trauma, *i.e.*, that they have no other cause. He confirmed that Philipp had no external marks or signs of trauma, that he did not look at any of the child's previous medical records in making his diagnosis, and that medical professionals do not understand how such trauma occurs.

35. Dr. Elliott, the ophthalmologist, operated on Philipp's eyes on November 7, 2003. He testified that the hemorrhages and detached retina were likely related to the bleeding in the brain. Given the extent of the damage, it was unlikely that Philipp would ever have useful vision. Dr. Elliott could not date the injuries other than to say that they happened at least a few weeks prior to surgery and that he did not think they could have been caused by birth trauma (or at least from normal birth).

36. Dr. Becker, the pediatric radiologist, testified that the October 4 CT scan showed that large areas of the brain had experienced severe trauma and/or lost blood supply, and that the sutures and skull fracture were spread wide by increased intracranial pressure. Dr. Becker testified that the skull fracture and areas of infarction (dead or dying tissue) represented two different injury patterns. The skull fracture was caused by the skull striking a solid object. However, the injuries inside the brain were diffuse and were not limited to the same side as the skull fracture (or the immediate opposite side), and thus could not be explained by impact. Dr. Becker felt that the brain injury was best explained as the result of a shaking occurring within 48 hours and more likely within 24 hours of the October 4 CT scan. Dr. Becker testified that, in making this diagnosis, she did not consult with the attending doctors or review any of the child's medical records or blood tests. Dr. Becker testified that she could not time the skull fracture, which could have been caused at birth, but that she would not expect a fracture from a natural, rather than a forceps, birth.

37. Weight loss. The prosecution relied heavily on pediatric records indicating that Philipp weighed 8 lbs 10 oz. on September 23 and the pediatrician's testimony that this weight gain confirmed that the child was "thriving." The medical records indicate that the child weighed approximately 6 lbs on admission to Mt. Clemens, indicating that he lost 2 lbs 10 oz. (or more than 30% of his body weight) between September 23 and October 3. I do not believe this weight loss is possible, even

with severe dehydration or even starvation. It is therefore my opinion that the 8 lb 10 oz weight was a clerical error of the type that is not uncommon in busy pediatric practices.

38. In infants, the standard criteria for dehydration are 5% loss of body weight for mild dehydration; 10% for moderate dehydration; and 15% for severe (life-threatening) dehydration. In this context, it is highly unlikely that an infant would have survived a 30% weight loss over a 10 day period. This is particularly unlikely since the grandparents and birth mother did not notice a weight loss on September 27-28, and the hospital personnel did not mention the extreme emaciation that would be expected from this type of weight loss, which is unlikely to have gone unnoticed (and unphotographed) by hospital personnel or law enforcement.

39. Given the child's clinical history, it seems more likely that the child was 6 lbs 10 oz, rather than 8 lbs 10 oz, on September 23. This would be consistent with the grandparent reports that the child seemed to be about the same weight on September 28 as he was after hospital discharge. It is also possible that he was closer to 7 lbs 4 oz, which was his weight on admission to Childrens Hospital after rehydration. If so, and if the 6 lb weight recorded on admission to Mt. Clemens is correct, the child lost 8-17% of his body weight, consistent with the reported dehydration.

40. In my opinion, the recorded weight of 7 lbs on August 29 is also erroneous. Since a healthy increase in the weight of an infant is ½ to 1 oz day, the increase in weight from 6 lbs 6 oz on August 23 to 6 lbs 8 oz on August 26 is credible. However, the reported increase from 6 lbs 8 oz to 7 lbs (nearly 3 oz a day) between August 26 and August 29 is not credible.

41. When one takes out the September 23 weight gain, the records describe a child who suffered some brain damage at birth, followed by a series of mini-seizures or mini-strokes, and a major hypoxic/ischemic event (venous sinus thrombosis) 24-72 hours before the first CT scan, likely triggered by infection, illness and/or dehydration. While it is not possible to trace the precise course of the brain damage without earlier CT scans and MRIs, the medical and clinical reports confirm this general progression.

42. Fracture. There is no evidence suggesting that Philipp's skull fracture resulted from abuse. As Dr. Becker made clear, this fracture cannot be dated. However, since fractures in infants are caused by impact and/or compression, a fracture of this size would generally be accompanied by some noticeable bruising or swelling. The only bruising and swelling noted in the medical records or caretaker reports is the bruising and swelling of the child's face immediately after birth. This suggests that the fracture was a birth injury, and that the subsequent feeding difficulties resulted from associated brain damage and/or oxygen deprivation, as evidenced by the child's dusky color after birth. While Dr. Becker is correct that fractures occur more often in assisted births, they are also reported,

albeit rarely, in natural births.

43. Ocular findings. The ocular findings indicate brain damage but do not suggest a causal mechanism. There are no indicators of external trauma, and the ocular findings are consistent with venous sinus thrombosis and increased intracranial pressure, as noted in the Childrens records. The relationship between increased intracranial pressure and intraocular hemorrhage, optic nerve sheath hemorrhage, vitreous hemorrhage and (in some instances) retinal detachment has been known since the 1970s. (Muller 1974, Vanderlinden 1974, Cogan 1975)

44. Radiology. I have reviewed a radiology report from Dr. Michael Krasnokutsky, which confirms the diagnosis of venous sinus thrombosis. His report included a PowerPoint based on the October 4 CT scan and October 30 MRI. Dr. Krasnokutsky's analysis is clear and easy to follow, and I agree with it entirely. The triangle shown on the October 4 CT scan (slide 1 and subsequent slides) and the location of the infarcts (along the superior saggital sinus) are characteristic of venous sinus thrombosis. The diagnosis of venous sinus thrombosis is confirmed in the October 30 MRI (slides 6-9), which shows thrombosed dural venous sinuses and likely recanalization (reopening) of a thrombosed transverse sinus. The location of thrombosis and infarcts confirms that they are not related to the earlier fracture.

45. Literature on venous sinus thrombosis. Thrombosis of the dural veins has been recognized in infants since the 1930s but has been increasingly diagnosed since the advent of CT scans and MRIs. I am attaching two articles from the New England Journal of Medicine (2001, 2004) that provide good overviews. DeVeber, G. et al, Cerebral Sinovenous Thrombosis in Children, N Eng J Med, 345;6 (2001); Ferriero, D., Neonatal Brain Injury, N Eng J Med. 351;19 (2004) (Atts. B and C).

46. The 2001 article reports on findings from the Canadian Pediatric Ischemic Stroke Registry, which was initiated in 1992 at 16 tertiary care centers in Canada. This study found that more than 40% of the 160 children diagnosed with sinovenous thrombosis were less than 3 months old. Acute systemic illness was present in 84% of neonates, with the most frequent illnesses being perinatal complications (51%) and dehydration (30%). Perinatal complications included hypoxia (lack of oxygen) at birth, premature rupture of the membranes, and gestational diabetes. Chronic systemic diseases were common in neonates (60%) and were diverse in nature. Cerebral parenchymal infarcts were present in 41% of the children. Predictors of adverse neurologic outcomes included seizures at presentation and infarcts.

47. The 2004 article confirms that the mortality rate from acute neurologic disorders of childhood, such as status epilepticus and stroke, is highest in infants under one year of age. Neonatal brain injury often eludes diagnosis since the clinical signs and symptoms are subtle and often attributed to developmental immaturity. Clinical symptoms include apnea, brachycardia, refractory seizures accompanied

by apneic episodes, shrill cry and jitteriness. Seizures may be manifested subtly as ocular movements such as deviation of the eyes or blinking, tongue or lip smacking or sucking, or sporadic moments of the extremities. Underlying damage may be associated with skull fractures occurring during delivery or as a result of blunt trauma to the mother's abdomen. Hypoglycemia, , hypocalcemia, hyponatremia, hypoxemia, acidosis and hyperbilirubinemia are often part of the underlying disorder. White matter disease is correlated with maternal infection, with the majority of infants with neonatal encephalopathy sustaining brain injury at or near the time of birth. Newborns usually have more than one risk factor, and perinatal complications such as hypoxic-ischemic events are often present. At least 30% of neonatal strokes are due to sinovenous thrombosis. Since many affected newborns seem healthy, without no obvious symptoms, diagnosis is often made only retrospectively. Prevalence data suggests that 8,000 babies are born in the U.S. each year with cerebral palsy caused by neonatal brain injury.

48. Virtually all of the identified risk factors and symptoms, including the risk factors for poor neurological outcome, are present in this case. These factors and symptoms include maternal infection, blood sugar variability and premature rupture of the membranes; age < 3 months; difficult birth evidenced by bruising, cut on forehead, and likely skull fracture; discoloration at birth, indicating lack of oxygen (hypoxia/ischemia); rapid eye blinking, tongue smacking and tremors of the extremities (August and September); hypoglycemia and infection (shortly after birth and on admission to Mt. Clemens); hyperbilirubinemia; dehydration; acidosis; seizures; infarctions; and subsequent diagnosis of cerebral palsy.

49. In this case, the diagnosis of trichomoniasis on 3/12/03 is of particular concern. Trichomoniasis is a sexually transmitted parasitic infection with increased risk of adverse outcome in pregnancy (early labor and low birth weights), with some case reports correlating trichomoniasis with infection, lethargy, poor appetite and/or respiratory failure in newborns. Trichomoniasis is also associated with chorioamnionitis, or inflammation of the membranes surrounding the fetus, which is associated with cerebral palsy and brain injuries in newborns, including full-term infants.

50. Shaking and other theories. Since the medical record indicates that the child's brain damage was natural rather than traumatic in origin, there is no need to consider shaking or blunt force impact. These diagnoses were very popular in the late 1990s and early 2000s but have always been highly controversial, and many of the underlying theories have been disproven.

51. At trial, Dr. Ophoven, the defense witness, was prohibited from testifying on the literature and advances in this field because she had not brought the articles with her. I am surprised that Dr. Ophoven was prohibited from testifying on the literature, particularly since the prosecution witnesses were permitted to testify to theories that were no longer accepted. Since Dr. Ophoven is well qualified, I expect that she would have addressed developments in the radiological, biomechanical and neuropathological literature on shaken baby syndrome and

pediatric head injury. By 2005, the literature was clear that shaking does not generate sufficient force to cause subdural or retinal hemorrhage in infants and that there is a wide range of alternative explanations, including infection, dehydration and venous sinus thrombosis, for symptoms previously attributed to shaking or nonaccidental injury. (Barnes 2002; Plunkett and Goldsmith 2004; Adams 2004; Lantz 2004; Bandak 2005; Leestma 2005).

52. This literature was often implicitly recognized by the prosecution's witnesses. For example, Dr. Becker testified that the fracture could be a birth injury and that the brain findings were consistent with lost blood supply, Dr. Ham testified that fractures could be caused by surprisingly little trauma, and numerous reports refer to ischemia, or lack of oxygen, rather than trauma. Yet the significance of these findings and the alternative diagnoses were never mentioned.

53. *Comments on trial testimony.* I found several aspects of the trial testimony to be particularly disturbing. First, the prosecution's medical witnesses testified that they did not review the child's medical records or clinical history before making their diagnoses. This is contrary to good medical practice. The medical literature establishes that there are many possible causes for brain damage, and that it is not possible to determine causation without a thorough review of the child's medical records, laboratory tests, medical imaging reports and clinical history.

54. Second, I am surprised that no one pointed out at trial that the testimony of the prosecution witnesses indicated that the major brain damage occurred while the child was in the hospital. Dr. Ham testified that the brain damage occurred 12-24 hours before the October 4 CT scan while Dr. Becker testified that the damage occurred 24-48 hours, but most likely 24 hours, before the scan. Since the scan was taken 32-33 hours after hospital admission, this indicates that the damage most likely occurred while the child was at Childrens Hospital. The damage could not have been as recent as 12 hours since an ultrasound taken at 8:01 a.m. on October 4 already showed abnormalities in the brain parenchyma (brain cells). However, the 24 hour estimate is consistent with the seizures and brain swelling noted in the Childrens records.

55. Third, it appears that, before trial, the prosecutor and defense attorney reached an agreement that birth injuries would be excluded at trial. Since the birth video and neonatal records confirmed that the child was bruised, cut and discolored after birth and required gavage (tube) feeding for a week, this eliminated the most obvious explanation for the skull fracture and subsequent deterioration.

56. Fourth, I would have expected more careful follow-up and instructions following the initial week-long hospitalization. As it is, the weight reports seem inaccurate, and there appears to have been no consideration, even in retrospect, that his feeding difficulties and tremors may have been related to birth injury and/or infection. In my opinion, the medical records and caretaker reports strongly suggest that this child was never well.

57. Fifth, after reading the transcript, I do not understand the State's theory of injury. Dr. Mok testified to natural disease processes, with no signs of trauma or blunt force injury. Dr. Becker testified that the child must have been shaken since there were no signs of blunt force injury other than a fracture, which was a separate injury and could not cause the diffuse brain damage shown on the CT scan. Dr. Ham and the prosecutor claimed that the fracture and diffuse brain damage were caused by blunt force trauma occurring on October 3 (the prosecutor) or October 4 (Dr. Ham). It is not possible to reconcile these contradictory theories.

58. Sixth, since there is a wide array of possible causes for Philipp's symptoms and findings, I do not understand why there was little or no consideration of the alternative diagnoses, including infection, dehydration, and childhood stroke. Since the symptoms for pre-existing brain damage and impending stroke are subtle and nonspecific, it is easy to understand why the significance of the child's symptoms (including twitching, tremors and rapid blinking) was not recognized prior to the child's collapse. However, in retrospect, these symptoms are classic precursors of venous sinus thrombosis, or childhood stroke.

59. As set forth above, the medical records do not contain any indications of trauma other than a skull fracture that most likely occurred at birth. Based on these records, it is my opinion that Philipp's brain damage is attributable to a progressive cascade of ischemic brain changes initiated by head injury, infection and/or hypoxic-ischemic damage that most likely began at birth. These injuries account for the peculiar mixture of clinical symptoms that started at birth and culminated in venous sinus thrombosis, most likely triggered by dehydration and infection, as documented in the hospital records.

60. I am providing an abbreviated list of references for each of the subject areas. Additional references will be provided on request.

I affirm under the penalty of perjury that the foregoing is true and correct to the best of my knowledge and belief.

James A. J. (Rex) Ferris, M.D., F.R.C.Path., F.F.Path.(I)., D.M.J.
Dated: September 8, 2008

REFERENCES

Shevell M et al, (1989), *"Neonatal Dural Sinus Thrombosis"*, Pediatric Neurology 5(3):161-5.

Barron T et al, (1992), *"Cerebral Venous Thrombosis in Neonates and Children"*, Pediatric Neurology 8:112-6.

Hartfield D et al, (1997), *"Iron Deficiency: A Cause of Stroke in Infants and Children"*, Pediatric Neurology 16(1):50-53.

DeVeber G et al, (2001), *"Cerebral Sinovenous Thrombosis in Children"*, New Eng J Med 345;6.

Carvalho, K et al, (2001), *"Cerebral Venous Thrombosis in Children"*, Journal of Child Neurology 16(8):574.

Lynch et al (2002), *"Report of the National Institute of Neurological Disorders and Stroke Workshop on Perinatal and Childhood Stroke"*, Pediatrics 109(1):116-123.

Heller et al (2003), *"Cerebral Venous Thrombosis in Children: A Multifactorial Origin"*, Circulation 108:1362-1367.

Ferriero D, (2004), *"Neonatal Brain Injury"*, New Eng J Med 351;19.

Sebire G et al, (2005), *"Cerebral venous sinus thrombosis in children: risk factors, presentation, diagnosis and outcome"*, Brain 128:477-489.

Roach E et al, (2008), *"Management of Stroke in Infants and Children, A Scientific Statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young,"* Stroke 39:2644-2691.

Wasay M et al, (2008), *"Cerebral Venous Sinus Thrombosis in Children: A Multicenter Cohort from the United States,"* Journal of Child Neurology 23(1):26-31.

Goldsmith W and Plunkett J, (2004), *"A Biochemical Analysis of the Causes of Traumatic Brain Injury in Infants and Children"*, American Journal of Forensic Medicine and Pathology, 25(2): 89-100.

Leestma J (2005), *"Case Analysis of Brain-Injured Admittedly Shaken Infants 54 Cases"*, 1969-2001, American Journal of Forensic Medicine and Pathology, 26(3): 199-212.

F.A. Bandak, (2005) *Shaken baby syndrome: a biomechanics analysis of injury mechanisms"*, Forensic Science International, June 30; 151(1): 71-9.

Clark BJ, (2001), Retinal Haemorrhages: *"Evidence of Abuse or Abuse of Evidence", The* American Journal of Forensic Medicine and Pathology, 22(4): 415-416.

Adams GGW, (2004) *"Forensic Science, Evidence Based Medicine and the "Shaken Baby Syndrome" – Retinal haemorrhages/Ocular manifestations"*, American Academy of Forensic Sciences, 2004.

Lantz, P and Stanton C, (2006), *"Postmortem Detection and Evaluation of Retinal Hemorrhages"*, American Academy of Forensic Sciences, 2006.

Barnes P, (2002), *"Ethical Issues in Imaging Nonaccidental Injury: Child Abuse,"* Topics in Magnetic Resonance Imaging 13(2):85-94.

Barnes P and Krasnokutsky M, (2007), *"Imaging of the Central Nervous System in Suspected or Alleged Nonaccidental Injury, Including the Mimics"*, Top Magn Reson Imaging 18(1):53-74.

Muller P and Deck J, (1974), *"Intraocular and optic nerve sheath hemorrhage in cases of sudden intracranial hypertension,"* J. Neurosurg. 41:160-166.

Vanderlinden R and Chisholm L, (1974), *"Vitreous hemorrhages and sudden increased intracranial pressure"*, J Neurosurg. 41:167-176.

Cogan, D, (1975), *"Ocular Involvement in Disseminated Intravascular Coagulopathy"*, Arch Ophthalmol 93:1-8.

Grether JK and Nelson KB, (1997), *"Maternal infection and cerebral palsy in infants of normal birth weight"*, JAMA 16;278(3):247-8.

Cotch MF et al, (1997), *"Trichomonas vaginalis associated with low birth weight and preterm delivery. The Vaginal infections and Prematurity Study Group,"* Sex. Transm. Dis. 24(6):353-60.

Wu YW and Colford, JM, (2000), *"Chorioamnionitis as a risk factor for cerebral palsy: A meta-analysis*", JAMA 284(23):2996-7.

Wu YW et al, (2003), *"Chorioamnionitis and Cerebral Palsy in Term and Near-Term Infants"*, JAMA 190:2677-2684.

Schwebke J and Burgess D, (2004), *"Trichomoniasis"*, Clinical Microbiology Reviews 17:794-803.

CURRICULUM VITAE

DR. JAMES ALEXANDER JOHNSTON FERRIS

NAME: James Alexander Johnston (Rex) FERRIS

OFFICE ADDRESS: 45 Phillips Drive, Oropi Downs
RD3 Tauranga 3173
New Zealand
Tel: 64-7-543-3014
Fax: 64-7-543-3034
E-mail rexferris@xtra.co.nz

DATE & PLACE OF BIRTH: 15 April, 1939, Belfast, N. IRELAND

NATIONALITY: Canadian/U.K. Citizen – New Zealand Resident

PREMEDICAL EDUCATION: Campbell College
Junior and Senior Exhibitioner

DEGREES AND DIPLOMAS

M.B., B.Ch., B.A.O.	Queen's University, Belfast, 1963
M.D. (by thesis)	Queen's University, Belfast, 1968
M.R.C. Path.	Member Royal College of Pathologists, 1980
F.R.C. Path.	Fellowship 1992
D.M.J.	Society of Apothecaries, London, 1971
L.M.C.C.	Medical Council of Canada, 1977
F.F.P.R.C.P.	Fellow, Faculty of Pathologists, Royal College of Physicians, Ireland
F.F. Sc.(Ind)-(Honorary)	Fellowship in Forensic Sciences, India, 1989
Registered Medical Practitioner	General Medical Council Great Britain and Ireland, 1963-75 Province of Ontario, 1975-1983 Province of Manitoba, 1977 Province of British Columbia, 1983-2004, Now Retired Life Member New Zealand Medical Council 2001-present (vocational registration in Pathology)

PRESENT APPOINTMENTS

Professor Emeritus of Forensic Pathology, University of British Columbia, Vancouver, Canada
Part-time Regional Forensic Pathologist, New Zealand
Ad Hoc Consultant Forensic Pathologist

PREVIOUS APPOINTMENTS

01/08/63 to 31/10/63	Casualty Officer, Royal Victoria Hospital, Belfast
01/11/63 to 31/01/64	House Physician to Prof. J.F. Pantridge, Royal Victoria Hospital, Belfast
01/02/64 to 30/04/64	House Surgeon to Mr. E. McMechan, Royal Victoria Hospital, Belfast
01/05/64 to 31/07/64	Resident Medical Officer, Plastic and Maxillo-Facial Unit, Royal Victoria Hospital (Throne Hospital)
01/10/64 to 30/09/67	John Dunville Fellow in Pathology, Queen's University of Belfast, under Prof. Sir John Biggart
01/10/66 to 30/09/67	Part-time Assistant in Forensic Medicine, Queen's University, Belfast, Under Prof. T.K. Marshall
01/10/67 to 30/09/68	Assistant State Pathologist Northern Ireland, Queen's University, Belfast under Prof. T.K. Marshall
01/10/68 to 31/03/69	Registrar in Hematology to Prof. M.G. Nelson, Royal Victoria Hospital, Belfast
01/04/69 to 31/07/73	Lecturer in Forensic Pathology, University of Newcastle upon Tyne
01/07/70 to 30/06/75	Consultant Pathologist to the Home Office for the North East of England
01/08/73 to 30/06/75	Senior Lecturer in Forensic Pathology, University of Newcastle upon Tyne.
01/08/73 to 30/06/75	Honorary Consultant Pathologist to the Newcastle University Hospitals, Newcastle upon Tyne.
01/08/75 to 31/12/76	Deputy Provincial Pathologist, Ministry of the Solicitor General, Ontario
01/08/75 to 31/12/76	Assistant Professor in Forensic Pathology, University of Toronto
01/01/77 to 31/10/77	Staff Pathologist, Health Sciences Centre, Winnipeg, Manitoba
01/01/77 to 31/10/77	Assistant Professor Pathology, University of Manitoba

01/11/77 to 30/06/83	Head, Dept. of Forensic Pathology Hamilton General Hospital, Ontario
01/11/77 to 30/06/83	Associate Professor, Forensic Pathology McMaster University , Hamilton, Ontario
01/07/83 to 31/08/88	Chief Forensic Pathologist British Columbia Coroners Service
01/07/83 to 31/08/97	Head of Forensic Pathology, Department of Laboratory Medicine, Vancouver Hospital and Health Sciences Centre.
01/07/83 to 31/12/99	Professor of Forensic Pathology, University of British Columbia
01/07/02 to 31/08/05	Consultant Forensic Pathologist, Auckland District Health Board.
01/01/05 to 30/06/06	National Advisor, Coronial Pathology Service, Ministry of Justice, N.Z.

DISTINCTIONS

2003	George Frank Memorial Lecture, McMaster University Hamilton, Ontario.
1998	Distinguished Lecturer Series Lecture, Department of Pathology, University of British Columbia
1996 - 1999	President, World Police Medical Officers Association in Forensic Medicine.
1986	Vice President International Academy of Legal and Social Medicine.
1985-87	Honorary President Canadian Society of Forensic Sciences.
1984-87	President, International Association of Forensic Sciences.
1977	Distinguished Scholar Lecturer, Queen's University, Belfast.
1975	Clinical Teacher of the Year, University of Newcastle upon Tyne.
1975	Awarded the Milburn Prize by the University of Newcastle upon Tyne for research in the Sudden Infant Death Syndrome.
1969	Serving Brother, Order of Saint John.

RESEARCH EXPERIENCE

1964-69 Mucosal patterns of the small intestine in a variety of disease states. Technical methods included tissue histochemistry, electron microscopy and the development of a peroral intestinal biopsy capsule custom made by Harland and Wolff to comply with the research requirements. Case material included in-hospital patients, autopsy cases and experimental animals.

1969-75 Sudden infant death syndrome. This work included an analysis of the development of the cardiac conducting system in the first six months of life and also a collaborative study with the Department of Microbiology, University of Newcastle upon Tyne correlating histological changes in the lungs with respiratory viruses.

A study of the cardiac conducting system in sudden cardiac deaths and in a variety of cardiomyopathies. A simplified method of examining the conducting system was developed and published.

Supervisor, Ph.D. thesis, Dr. S.R.M. Kendeel, "Pathogenesis of Sudden Infant Death Syndrome", University of Newcastle upon Tyne, 1976.

1975-82 Collaborative studies with the Civil Aviation Medical Unit and the Civil Aviation Safety Board, including:

1. Tissue lactate levels, pulmonary fat embolism and survival time.
2. Incidence of alcohol related heart and liver disease in aviation fatalities.
3. Injury pattern analysis in a variety of mass disaster cases including the Arrow Air Accident at Gander, the Schefferville Accident and the USS Iowa gun-turret explosion.

1977 Development of an experimental model for toxic cardiomyopathy using Cantharidine.

1977-82 Histological features of alcohol related heart disease.

Incidence of cardiac contraction-band myocytolysis in sudden death.

Scanning electron microscopic features of experimental drowning.

1983-93 Application of D.N.A. genetic typing to forensic science with Dr. A. Autor. Funded by research grants from the Law Foundation of British Columbia and the Ministry of the Attorney General of British Columbia

Incidence of coronary artery disease in young adults and in cocaine related deaths with Drs. H. Mizgala and L. Gray.

1994-1998 Supervisor, Ph.D. Thesis, Dr. Lori Bonnycastle, "Allelic Frequencies of Two DNA Restriction Fragment Length Polymorphism Systems Collected from an
1996-1999 High Resolution Nuclear Image Cytometry to measure nuclear degradation as a method for the determination of time since death.

Supervisor of Ph.D. Student Laura Johnson studying the application of comet assay as a means of correlating nuclear degradation and time since death.

Current Analysis of pulmonary microvascular changes in severe obesity.

Mechanisms of head injury in infants and children.

Undefined Population: Application to DNA Profiling".

Research Grants:

$95000.00 annual grant to support time since death research funded by Biomax Technologies Inc., 1997-1999

PATENTS HELD

UK Patent GB 2 249 627 B. 'Method of Establishing Identity'.
Inventors - Cheung, L.L.C., McNeil, B.K., Autor, A.P., Ferris, J.A.J.

UNIVERSITY COMMITTEES

Former Member Medical Education Committee and Board of Examiners, Faculty of Medicine, University of Newcastle upon Tyne.

Former Member Medical Education Committee McMaster University Medical School.

Former Chairman, Student Affairs McMaster Medical School with overall responsibility for student counseling, the student advisor program and the financial aid program. This included a complete reorganization of the loans and bursary schemes and the establishment of a financial committee.

Former Member McMaster University Presidential Task Force on scholarships and bursaries to develop new guidelines for financial awards.

Former Chairman, Task Force Student Advisor Program, Dept. Nursing McMaster Faculty of Health Sciences.

Member Medical Faculty Admissions Selection Committee U.B.C.

Former Member Medical Faculty Trauma Committee U.B.C.

Former Member Medical Admissions Policy Committee U.B.C.

OTHER COMMITTEES

Former Co-Chairman Medicolegal Planning Committee, Medical-Legal Society of B.C.

Past-President, Medical Legal Society of British Columbia

Former Member Task Force on Ministry, Christ Church Cathedral, Vancouver

Former Member Christ Church Cathedral Parish Committee

Former Member Federal-Provincial Task Force to develop guidelines for Health Care Institutions for the management of victims of assault, abuse and neglect. (published)

TEACHING RESPONSIBILITIES

Director of Graduate Studies course in Forensic Pathology at University of British Columbia. (Path. 575)

Forensic Pathology lecture series to M.D. students at University of British Columbia. (Path. 425)

Forensic Pathology Lecture Series, British Columbia Institute of Technology

Previous Director of Canadian Association Pathology Forensic Pathology workshop on interpretation of wounds.

Regular lectures to police, coroners, lawyers, other professional organizations, community groups and at the Justice Institute of British Columbia.

University of Auckland Forensic Sciences Course 701, Forensic Pathology lectures

PUBLICATIONS

1. Ferris, J.A.J. (1968) "The Intestinal Mucosa in Disease States". Thesis, Queen's University, Belfast.

2. Glasgow, J.F.T. and Ferris, J.A.J. (1968) "Encephalopathy and Visceral Fatty Infiltration of Probable Toxic Aetiology". Lancet 1, 451.

3. Ferris, J.A.J. and Aherne, W.A. (1971) "Cartilage in Relation to the Conducting Tissue of the Heart in Sudden Death". Lancet, 1, 64.

4. Ferris, J.A.J. and Aherne, W.A. (1971) "Fibrocartilage in the Heart" (letter). Lancet 1, 802.

5. Ferris, J.A.J. (1971) "The Cardiac Conducting System of Infants." Proceedings 13th International Congress of Paediatrics, Vienna, 9, 81.

6. Ferris, J.A.J. (1973) "The Intestinal Mucosa in Thyrotoxicosis: A Light and Electron Microscopic Assessment". Irish Journal of Medical Sciences 141, 3.

7. Ferris, J.A.J. and Stockdale, R.E. (1972) "The Bluebell Woods Case: A Problem of Identification". Journal of Forensic Science Society, 12, 339.

8. Ferris, J.A.J. (1972) "Cot Deaths - Why Not the Heart?" Medicine, Science and the Law, 12, 173.

9. Ferris, J.A.J. (1972) "The Conducting Tissue in Sudden Death" (abstract). Sixth International Meeting Forensic Sciences, 110.

10. Ferris, J.A.J. (1972) "Cot Death Symposium - Introduction". Journal of Forensic Science Society, 12, 573.

11. Ferris, J.A.J. (1972) "The Heart in Sudden Infant Death". Journal of Forensic Science Society, 12, 591.

12. Ferris, J.A.J. (1973) "An Honest Opinion". Journal of Forensic Science Society, 13, 75.

13. Ferris, J.A.J. (1973) "The Conducting Tissue in Hypertrophic Obstructive Cardiomyopathy". Beitrage zur Pathologie, 148, 296.

14. Ferris, J.A.J. (1973) "Hypoxic Changes in the Conducting Tissue of the Heart in the Sudden Death in Infancy Syndrome". British Medical Journal, 2, 23.

15. Ferris, J.A.J. (1973) "The Pathologist and the Scene of the Crime". The Police Surgeon, 3, 69.

16. Ferris, J.A.J., Aherne, W.A., Locke, W.S., McQuillen, J. and Gardner, P.S. (1973) "Sudden and Unexpected Deaths in Infants: Histology and Virology". British Medical Journal, 2, 439.

17. Ferris, J.A.J. and Parkin, J.M. (1973) "Occlusions of the Atrioventricular Nodal Artery in Cogenital Heart Block". Beitrage zur Pathologie, 149, 311.

18. Ferris, J.A.J. and Maclennan, J.R. (1973) "A Simplified Method for Examining the Conducting Tissues of the Heart". Medicine, Science and Law, 13, 285.

19. Ferris, J.A.J. (1974) "Conducting Tissue Changes in Sudden Death". Medicine, Science and Law, 14, 36.

20. Ferris, J.A.J. (1974) "Forensic Problems in Medical Records". Medical Record, 15, 8.

21. Ferris, J.A.J., Stainthorp, M.C., and Kendeel, S.R. (1974) "Hypoxic Changes in the Myocardium in Sudden Infant Death and Their Relationship to Respiratory Tract Findings. Actes des 34th Congres International de langue Francaise, de Medecine Legale and de Medecine Sociale, TP/AP.

22. Ferris, J.A.J. and Stoddart, J.C. (1974) "Threshold for Oxygen Pneumonitis". British Medical Journal, 2, 384.

23. Ferris, J.A.J. and Kendeel, S.R. (1974) "Sudden Infant Death" (letter). British Medical Journal, 2, 559.

24. Ferris, J.A.J. (1974) "Problems in Interpretation of Lung Histology". Proceedings of Francis Camps International Symposium on Sudden Infant Death, Toronto, 21.

25. Ferris, J.A.J. and Kendeel, S.R. (1975) "Fibrosis of the Conducting Tissue in Infarct". Journal of Pathology, 117, 123.

26. Ferris, J.A.J. (1975) "That Muddy Field". Journal of Forensic Science Society, 15, 91.

27. Downham, M.A.P.S., Gardner, P.S., McQuillen, J., and Ferris, J.A.J. (1975) "Role of Respiratory Viruses in Childhood Mortality". British Medical Journal, 1, 235.

28. Ferris, J.A.J. (1976) "The Pathology of Fatal Dysrhythmias". Journal of Forensic Sciences, 8, 23.

29. Kendeel, S.R. and Ferris, J.A.J. (1977) "The Sudden Infant Death Syndrome - A Review of the Literature". Journal of Forensic Sciences Society, 17, 223.

30. Levene, D.L. and Ferris, J.A.J. (1977) "Midseptal Hypertrophic Non-Obstructive Cardiomyopathy". American Heart Journal, 94, 769.

31. Kendeel, S.R. and Ferris, J.A.J. (1977) "Pulmonary Vascular Changes in S.I.D.S". Journal of Clinical Pathology, 39, 487.

32. Kendeel, S.R. and Ferris, J.A.J. (1978) "Sudden Infant Death Syndrome" (letter). Journal of Clinical Pathology, 31, 198.

33. Rabkin, S.W., Friesen, J.M., Ferris, J.A.J. and Fung, H.Y.M. (1978) "A Model of Cardiac Arrhythmias and Sudden Death: Cantharidin Induced Toxic Cardiomyopathy" (abstract). Federated Proceedings, 37, 419.

34. Friesen, J.M., Ferris, J.A.J., Rabkin, S.S. and Fung, H.Y.M. (1979) "Pathological Features of Cantharidin Induced Toxic Cardiomyopathy". Forensic Science International, 13, 187.

35. Ferris, J.A.J. and Rice, J. (1979) "Drug Induced Myocarditis: A Report of Two Cases". Forensic Science International, 13, 261.

36. Ferris, J.A.J. and Friesen, M.M., (1979) "Definitions of Infarction and Necrosis". Forensic Science International, 13, 253.

37. Rabkin, S.W., Friesen, J.M., Ferris, J.A.J. and Fung, H.Y.M. (1979) "A Model of Cardiac Arrhythmias and Sudden Death Cantharidin Induced Toxic Cardiomyopathy". Journal of Pharmacology and Experimental Therapeutics, 210, 43.

38. Ferris, J.A.J. and Thompson, P. (1981) "A Histological Assessment of the Incidence of Alcoholic Cardiomyopathy in Subjects with Alcohol Associated Liver Disease". Canadian Society of Forensic Sciences Journal, 14, 113.

39. Ferris, J.A.J. and Thompson, P. (1981) "A Histological Assessment of the Incidence of Alcoholic Cardiomyopathy in Subjects with Alcohol Related Liver Disease". Journal of Forensic Science Society, 21, 100. (Abstract 9th Meeting International Association of Forensic Sciences, Bergen, 1981).

40. Chiu, S., Ferris, J.A.J., Johnson, R., and Mishra, R.K. (1982) "C.N.S. Putative L-Prolyl-L-Leucyl-Glycinamide (PLG) Receptors, Brain and Lymphocyte Dopamine Receptors". Neuropsychopharmacology. Vol. 6.

41. Chiu, S., Wong, Y.W., Ferris, J.A.J., Johnson, R., and Mishra, R.K. (1983) "Binding Studies of L-Prolyl-L-Leucyl-Glycinamide (PLG), A Novel Antiparkinsonian Agent in Normal Human Brain". Pharmacological Research Communications, 15, 41-51.

42. Banna, M., Ferris, J.A.J., McLean, L. and Thompson, P. (1983) "Anatomical-Radiological Study of the Borderline Sella". British Journal of Radiology, 56, 1-5.

43. Ferris, J.A.J. (1983) "Murder by Fright". Proceedings 1st Asian-Pacific Congress on Legal Medicine and Forensic Sciences, 420-421.

44. Ferris, J.A.J. (1984) "Murder by Fright". Acta Medicinae Legalis et Socialis, 34, 32.

45. Ferris, J.A.J. (1983) "Medical Aspects of Fire Deaths - Coroner's Concern". 3rd Symposium on Combustibility and Plastics, 59.

46. Ferris, J.A.J., Ashworth, E.J. and Morison, D.H., (1984), "Cardiorespiratory Collapse During Spinal Anaesthesia in a Case of Malignant Hyperthermia Syndrome". Canadian Society of Forensic Sciences Journal, 17, 19-21.

47. Ferris, J.A.J. (1985) "Death by Fright: A Question of Causation". Canadian Society of Forensic Sciences Journal, 18, 92-96.

48. Tyler, M.G., Kirby, L.T., Wood, S., Vernon S. and Ferris, J.A.J. (1986) "Human Blood Stain Identification and Sex Determination in Dried Blood Stains using Recombinant DNA Techniques". Forensic Science International, 31, 267-272.

49. Antonenko, N. and Ferris, J.A.J. (1987) "Diatoms and Drowning." Canadian Society of Forensic Sciences Journal, 20, 1-11.

50. Ferris, J.A.J. (1987) "Forensic Science and the Justice System in the Late 20th Century", Journal of Forensic Science Society, 147-155.

51. Bastien, B., Gray, L.H., and Ferris, J.A.J. (1987) "The Application of Computer Photo-Enhancement and Digitalization to the Determination of Age of the Os Pubis". Canadian Society of Forensic Sciences Journal, 20, 160. (Abstract)

52. Barker, I., Ferris, J.A.J., Adams, M. and Martin, B. (1987) "The Dingo Baby Case - Forensic Science on Trial". Canadian Society of Forensic Sciences Journal, 20, 15. (Abstract)

53. Gilchrest, E.J., McNeil, K., Kirby, L.T., Ferris, J.A.J. and Autor, A.P. (1987) "Quantitative and Qualitative Analysis of DNA From Forensic Specimens". Canadian Society of Forensic Sciences Journal, 20, 32. (Abstract)

54. LaPrairie, A.J.P., Ferris, J.A.J. and Gray, L.H. (1987) "The Application of Delipidization Techniques to Diatom Examination of Bone Marrow Samples". Canadian Society of Forensic Sciences Journal, 20, 232. (Abstract)

55. Antonenko, N., Gray, L.H. and Ferris, J.A.J. (1987) "Diatoms and Drowning". Canadian Society of Forensic Sciences Journal, 20, 234. (Abstract)

56. McNeil, K., Gilchrest, E.J., Kirby, L.T., Autor, A.P. and Ferris, J.A.J. (1987) "Use of Repetitive Sequence DNA Probes to Detect Unique Highly Polymorphic Genomic Loci Fragment Patterns". Canadian Society of Forensic Sciences Journal, 20, 58. (Abstract)

57. Ferris, J.A.J. And Gray, L. (1987) "Coronary Artery Avulsion Injury". Canadian Society of Forensic Sciences Journal, 20, 268. (Abstract)

58. Sloan, J.H., Reay, D., Ferris, J.A.J., Kellermann, A., Gray, L.H., Rice, C.L., and LoGerfo, L. (1987) "Epidemiology of Homicides in Seattle, Washington and Vancouver, British Columbia". Canadian Society of Forensic Sciences Journal, 22, 276. (Abstract)

59. Ferris, J.A.J. (1987) "Can Forensic Sciences Serve as a Non Medical Discipline?". Uses of the Forensic Sciences,14-22, Scottish Academic Press.

60. Sloan, J.H., Kellerman, A.L., Reay, D.T., Ferris, J.A.J., Koepsell, T., Rivara, F.P., Rice, C., Gray, L., LoGerfo, J. (1988) "Handgun Regulations, Crime, Assaults, and Homicide". The New England Journal of Medicine, 319, 1256-62.

61. Ferris, J.A.J. (co-author and contributor) (1989) "Health Care Related to Abuse, Assault, Neglect and Family Violence - Guidelines". Published by Health and Welfare, Canada.

62. Sloan, J.H., Rivara, F.P., Reay, D.T., Ferris, J.A.J.,Kellermann, A.L. (1990) "Firearm Regulations and Community Suicide Rates: A Comparison of Two Metropolitan Areas". New England Journal of Medicine, 322, 369-373.

63. Little, D. and Ferris, J.A.J. (1990) "Determination of Human Immunodeficiency Virus Antibody Status in Forensic Autopsy Cases in Vancouver Using a Recombinant Immunoblot Assay". Journal of Forensic Sciences, 35, 1029-1034.

64. Mizgala, H.F., Gray, L.H., Ferris, J.A.J., Bociek, V., Allard, P., (1991) "Extent of Coronary Artery Narrowing in 329 Cases of Unexpected Death, Age 40 Years and Under". Modern Pathology, 4:19a (Abstract).

65. Mizgala, H.F., Gray, L.H., Ferris, J.A.J., Virmani, R., Bociek, V., Allard, P. (1992) "Extent of Coronary Luminal Narrowing in 20 Cases of Cocaine Deaths Under Age 40 Years". Modern Pathology, 5:22a (Abstract).

66. Mizgala, H.F., Gray, L.H., Ferris, J.A.J., Harrison, A., Palcic, B., Bociek, V., and Hughes, L. (1992) "Comparison of Coronary Atherosclerosis in 26 Cocaine Deaths with Age and Sex Matched Trauma Controls". Canadian Journal of Cardiology, 8 (Suppl.B), 128.

67. Mizgala, H.F., Gray, L.H., Ferris, J.A.J., Bociek, V., Allard, P., and Davies, C., (1993) "Coronary Artery Luminal Narrowing in the Young with Sudden Unexpected Death: A Coroner's Autopsy Study in 350 Subjects Age 40 Years and Under". Canadian Journal of Cardiology, 9, 33-040.

68. Ferris, J.A.J. (1998) "The Forensic Pathology of Victims of an Explosion" a chapter for a textbook on The Forensic Investigation of Explosions, editor A.D. Beveridge, Publisher Taylor and Francis Ltd., London and New York.

69. Ferris, J.A.J., Whitehead, P., Abbott, D., Ferris, A., McManus, B.M., MacAuley, C., Guillaud, M., Doudkine, A., and Payne, P.W. (1998) "High Resolution Image Cytometry to Quantitate Time Since Death", Proceedings 6th INPALMS Congress (in press)

70. Payne, P.W., Johnson, L.A., Haskins, D., Baccino, E. and Ferris, J.A.J. (1999) "Estimation of time since death by image cytometric analysis of cell nuclei" Journal of Clinical Forensic Medicine, 6, 197 (abstract)

71. Johnson, L.A., Payne, P.W., Haskins.D., Baccino, E. and Ferris, J.A.J. (1999) "Estimation of time since death by single cell gel electrophoresis" Journal of Clinical Forensic Medicine, 6, 197 (abstract)

72. Ferris, J.A.J., (2000) "Causes of death (h) Asphyctic deaths" a chapter in Encyclopedia of Forensic Sciences, Publisher Academic Press, London, Editor in Chief, Jay Siegel.

73. Johnson, L.A. and Ferris J.A.J. (2002) "A biophysical analysis of postmortem DNA degradation utilizing single-cell gel electrophoresis", Forensic Science International, 126(1), 43-47.

74. Ferris, J.A.J. (2004) "Evidential Issues in Shaken Baby Syndrome" Proceedings of 7th Indo-Pacific Congress on Legal medicine and Forensic Sciences (abstract 146)

75. Ferris, J.A.J. (2005) "The Adult Autopsy" a chapter in Encyclopedia of Forensic and Legal Medicine, Publisher Academic Press, London.

76. Johnson, L.A. and Ferris, J.A.J. (2005) "Single cell electrophoresis in determining cell death: Potential for use in organ transplant research" Journal of Biochemical and Biophysical Methods, 63, 53-68.

77. Ferris, J.A.J. (2006) "Forensic Pathology of Traffic Accident Reconstruction" a chapter in "Evidence in Traffic Accident Investigation and Reconstruction" by R.W. Rivers, published by CC Thomas, Springfield, Il.

78. Ferris, J.A.J. (2006) "Code of Practice and Performance Standards for Forensic and Coronial Pathologists", 1st Edition, Ministry of Justice, New Zealand.

79. Ferris, J.A.J. (2008) "Relationship of Body Weight and Sudden death" a chapter for 'Essentials of Autopsy Practice, Topical Developments, trends and advances': edited by GN Rutty, published by Springer-Verlag London Ltd.

IN PREPARATION

Ferris, J.A.J. "The Forensic Pathology of Domestic Violence"
Ferris, J.A.J. "Morbid Obesity and Asthma"
Ferris, J.A.J. "Shaken Baby Syndrome – Fact or Fiction"

FORENSIC EXPERIENCE:

Performed approximately 9500 medico-legal autopsies, including over 900 cases of homicides. In addition, has acted in a consultant capacity for both Prosecution and Defence, in over 450 cases of homicide. Since September 1997 until July 2002 was a part-time Consultant Forensic Pathologist with approximately 25% of cases involving Civil litigation, 25% opinion evidence for the Prosecution and 50% for the Defence. Over 70 Pediatric Forensic cases for both Prosecution and

Defence, including child abuse, murder and sexual assault. From July 1, 2002 – August 31, 2005 was a full-time Consultant Forensic Pathologist in Auckland, New Zealand. Following retirement was the National Advisor for Coronial pathology to the NZ Ministry of Justice until July 2006 and has since continued an independent consulting practice.

Has given expert evidence to courts at all levels in a variety of jurisdictions, including Northern Ireland, England, Newfoundland, Quebec, Ontario, Manitoba, Saskatchewan, Alberta, Yukon Territory, Colorado, Washington State, Wisconsin, Oregon, Hong Kong, British Columbia, Australia and New Zealand.

Given expert opinions and evidence in a variety of industrial and civil actions.

Clinical Forensic Medicine practice has included the regular examination of alleged victims of torture applying for refugee status in Canada.

Former Member of a Canadian Federal-Provincial Task Force on Investigation of Criminal Injuries - Report published.

Criminal Personality Profiles and Crime Scene Assessment Course, Michigan State University.

Consultant Forensic Pathologist to the Royal Commission of Enquiry into the Chamberlain Convictions (the Dingo Baby Case), Commonwealth of Australia.

Consultant Forensic Pathologist to the Defence in the Milgaard Case (Saskatchewan, Canada).

Expert Witness to the Commission of Enquiry into the Wrongful Conviction of David Milgaard, Saskatchewan, Canada, 2006

Consultant Forensic Pathologist to the Defence in the Morin Case (Ontario, Canada).

Consultant Forensic Pathologist Department of National Defence, Canada, concerning the exhumation and investigation of the shooting death of Ahmed Afraraho Aruush in Belet Huen, Somalia (The Somalia Affair).

Consultant Forensic Pathologist to the Special Prosecutor and the Defence in R. v. Clayton Johnson (Nova Scotia, Canada).

Consultant Forensic Pathologist to the Defence in R. v. Ronald Dalton (St. John's Newfoundland)

Consultant Forensic Pathologist to the Defence in R. v. Louise Reynolds (Kingston, Ontario)

Consultant Forensic Pathologist to the RCMP Task Force re: Air India Disaster

Consultant Forensic Pathologist to the Attorney General of New Zealand, re: R. v. David Bain with presentation of evidence to New Zealand Court of Appeal.

Consultant Forensic Pathologist to the Defence in R. v. Pauca Appeal with presentation of evidence in the Court of Appeal, Royal Courts of Justice, London

Visiting Consultant Forensic Pathologist, Department of Forensic Pathology, Auckland New Zealand, conducting routine medico-legal autopsies and an independent review of Forensic Pathology Services relating to staff work loads and quality assurance.

Consultant Pathologist Canadian Transportation Safety Board including an analysis of the injury patterns in the Arrow Air Disaster at Gander, Newfoundland and the USS Iowa gun-turret explosion.

Consultant Forensic Pathologist, Attorney General, State of Washington, re Guidelines for Judicial Hanging in the State of Washington.

Member of NZ Ministry of Justice Task Force on development of a National Forensic Pathology Service and National Advisor to the NZ MoJ on Forensic Pathology until July 2006.

Consultant Forensic Pathologist to the Home Office Disciplinary Hearing, re: Dr. Michael Heath.

Consultant Forensic Pathologist to New South Wales Medical Board, re: Dr. Allan Cala Professional Standards Committee Inquiry.

MEMBERSHIP OF ORGANIZATIONS AND PROFESSIONAL SOCIETIES

1. Honorary Life Fellow and Council Member, British Association in Forensic Medicine.
2. Former Canadian Liaison Officer and Council Member, Forensic Science Society.
3. Member American Academy of Forensic Sciences.
4. Fellow of Royal College of Pathologists (U.K.).
5. Former Chairman Board of Directors, Canadian Society of Forensic Sciences.
6. Former Member Board of Directors, Canadian Society of Forensic Sciences.
7. Former Member International Study Group for the Investigation of Sudden Natural Deaths.
8. Editorial Board, Forensic Science International.
9. Past Editorial Board, Journal of Canadian Society of Forensic Sciences.
10. Past President and former Member of Executive, Medical-Legal Society of B.C.
11. Former Secretary, North of England Medico-Legal Society.

12. St. John Ambulance Brigade: Former Deputy Provincial Surgeon Ontario, Former Area Commissioner Newcastle upon Tyne, Former Divisional Surgeon Transport Division, Northern Ireland.

13. Major, Royal Army Medical Corps, T.A.V.R.O.

14. Life Member Indian Society of Forensic Sciences.

15. Editorial Consultant, International Journal of Legal Medicine.

16. Editorial Board, Legal Medicine (Japanese Society of Legal Medicine.

GUEST LECTURES and PRESENTATIONS (Since March 1985)

Toronto Academy of Medicine, Toronto, Canada

Indian Society of Forensic Sciences, Madras, India

Australian Forensic Science Society, Melbourne, Australia

Australasian and Pacific Area Association of Police Medical Officers, Sydney, Australia

University of Strathclyde, Glasgow, Scotland

Brown University, Dept. of Continuing Medical Education, Providence, Rhode Island

Second Indo-Pacific Association of Forensic Sciences, Columbo, Sri Lanka

Opening address to the Criminology Section of Australia and New Zealand Association of Advancement of Science, Palmerston North, New Zealand

Death Investigation Seminar, University of Washington, Department of Continuing Education

B.C. Crime Prevention Association, Penticton, British Columbia

Joint Committee on Aviation Pathology Annual Meeting, Toronto, Ontario

Canadian Society of Forensic Sciences Annual Meeting, Toronto, Ontario

British Columbia Institute of Technology guest lecture, Burnaby, British Columbia

Provincial Court Judges Seminar, Vancouver, British Columbia

Death Investigation Seminar, Department of Justice, Yukon

6th Paulo Foundation Symposium on Investigation of Sudden Death, Helsinki, May 1989.

Third Indo-Pacific Congress, Madras, 1989, plenary lecture.

Pacific Northwest Society of Pathologists, Vancouver, September, 1989.

Ontario Society of Medical Technologists, Hamilton, Ontario, September, 1990

International Association of Forensic Sciences, Adelaide, Australia, October, 1990

World Police Medical Officers Conference, Auckland, New Zealand, November, 1990

Aviation Medicine Seminar, Vancouver, November, 1990

Canadian Society of Toxicologists, Montreal, December, 1990

Pacific Northwest Forensic Studies Seminar, Vancouver, October 1992

Australasian and Pacific Area Association of Police Medical Officers, Hong Kong, October 1992

University of Hong Kong, Department of Pathology, Guest Lecture, October 1992

Civil Aviation Medicine Seminar, Vancouver, November 1992

Post-graduate Medical Seminar, Yorkshire, England, March 1993

R.C.M.P. Training Seminar, Vancouver, April 1993

University of Tokyo, Japan, July 1993

Canadian Identification Society, Vancouver, July 1993

Keynote address International Association of Forensic Sciences, Dusseldorf, Germany, August 1993

Hong Kong University, Dept. of Pathology, Hong Kong, October 1993

Medico-Legal Society of Hong Kong, October 1993

Aviation Medicine Seminar, Vancouver, October 1993

National Defender Investigator Association Conference, Seattle, November 1993

Canadian Society of Laboratory Technologists, Vancouver, June 1994

British Association in Forensic Medicine, Cambridge, England, July 1994

Florida Public Defenders Association Conference, Jacksonville, Florida, August 1994.

British Columbia Crime Prevention Association, Vancouver, Sept.1994.

Sudden Cardiac Death Seminar, International Academy of Pathology, Hong Kong, October 1994.

Australian and New Zealand Society of Forensic Sciences International Meeting, Auckland, November 1994, Key-Note Lecture

British Association of Police Surgeons Conference, Bristol, England, May 1995.

British Columbia Association of Medical Laboratory Technologists, Cranbrook, B.C., September 1995.

Trauma Cycle 5, Vancouver, B.C., October 1995, Plenary Speaker.

World Police Medical Officers Conference, Kumamoto, Japan, August 1996.

International Association Forensic Sciences Conference, Tokyo, Japan, August 1996.

Medico-Legal Society, Belfast, N. Ireland, October 1996.

Medico-Legal Society of Hong Kong, July 1998.

First Joint British Congress of Forensic Sciences, Glasgow, July 1998.

Indo Pacific Conference in Legal Medicine and Science, Kobe, Japan, July 1998

International Symposium on Forensic Sciences, Adelaide, Australia (Keynote Speaker), October 1998

Victorian Institute of Forensic Medicine, Melbourne, Australia, October 1998

Canberra Hospital, Canberra, Australia, October 1998

Department of Forensic Pathology, Westmead, Sydney, Australia, October 1998

British Association in Forensic Medicine, Cardiff, Wales, November 1998

Trauma Cycle Course, VHHSC, Vancouver, March 1999

Level 3 Fire Investigator's Course, Penticton, B.C., October 1999

Police Surgeons Association Fall Seminar, Belfast, N.I., October 1999.

Brock House Society, Vancouver, November 1999.

Royal Society of Medicine, London, Opening Address Symposium on Miscarriages of Justice, January 2000.

Joint Meeting of the Medico-Legal and Criminology Societies of Hong Kong, February 2000.

Department of Pathology, Hong Kong University, February 2000.

Plenary Speaker, 15th International Symposium, Australian and New Zealand Society of Forensic Sciences, Gold Coast, Australia, March 2000.

Institute of Environmental Science and Research (ESR), Forensic Science Division, Auckland, New Zealand, March 2000.

Department of Pediatric Pathology, British Columbia's Children's Hospital, Vancouver, B.C.

Plenary Session Speaker at British Association of Police Surgeons Conference, Swindon, England, May 2001.

New Zealand Forensic Science Society, Auckland, New Zealand, June 2001.

Indo Pacific Conference on Medicine Law and Science, Melbourne, September 2001.

World Police Medical Officers Conference, Sydney, Australia, March 2002.

Medico-Legal Society of British Columbia, Vancouver, May 2002.

Crime Scene Coordinators Course, NZ Police, Christchurch, October 2002.

British Association in Forensic Medicine, Glasgow, Scotland, November 2002.

Hamilton Society of Pathologists, Hamilton, Ontario, Canada, April 2003.

George Frank Memorial Lecture, McMaster University, Hamilton, Ontario, Canada, April 2003.

Australasian Coroner's Conference, Christchurch, New Zealand, October, 2003.

Royal Australasian College of Pathologists Conference, Auckland, New Zealand, October 2003.

British Association in Forensic Medicine, Cardiff, Wales, November 2003.

Australia and New Zealand Forensic Science Society Conference, Wellington, N.Z., March, 2004.

British Association in Forensic Medicine, Aberdeen, Scotland, July 2004.

New Zealand Institute of Laboratory Technology, Hamilton, N.Z., August 2004.

International Association of Forensic Sciences, Hong Kong, August 2005.

Fifth Biennial Coroner's Conference, Rotorua, N.Z., September, 2005.

British Association in Forensic Medicine, Penrith, England, June 2006.

Cross Channel Conference on Forensic Medicine, Torquay, England, June 2007

EXTRACURRICULAR ACTIVITIES

Sailing: Certified by the Canadian Yachting Association in basic, intermediate and advanced sailing, and coastal and celestial navigation. Winner PHRF Division III Victoria-Maui International Yacht Race, 1992.

Former Member of The Royal New Zealand Yacht Squadron, The Royal Ocean Racing Club and The Royal Ulster Yacht Club. Member of Mount Maunganui Golf Club, Tauranga, New Zealand.

Former Member of the Anglican Cathedral Choirs of Hamilton, Ontario and Vancouver, B.C.

Former Medical Officer 500 Motor Racing Club, Ireland and Former Member Ontario Race Physicians. Medical Officer Vancouver Molson INDY, 1990 & 1991.

March 2008

the NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MEDICAL PROGRESS

Neonatal Brain Injury

Donna M. Ferriero, M.D.

From the Departments of Neurology and Pediatrics, University of California at San Francisco, San Francisco. Address reprint requests to Dr. Ferriero at the Departments of Neurology and Pediatrics, University of California at San Francisco, 521 Parnassus Ave., C215, San Francisco, CA 94143-0663, or at dmf@itsa.ucsf.edu.

N Engl J Med 2004;351:1985-95.
Copyright © 2004 Massachusetts Medical Society.

THE MORTALITY FROM ACUTE NEUROLOGIC DISORDERS OF CHILDhood, such as status epilepticus and stroke, is highest in infants under one year of age.[1,2] Certain forms of newborn brain injury, such as stroke, have an incidence as high as 1 in 4000 live births.[3] More than 95 percent of infants who have a stroke survive to adulthood, and many have residual motor or cognitive disabilities. Stroke and other forms of brain injury have a considerable effect on surviving babies, their families, and society. Since many adult diseases have their origins in prenatal or early postnatal life,[4] delineating the mechanisms underlying the vulnerability of the developing central nervous system to diverse insults should lead to new therapeutic interventions that affect outcome.

The erroneous view that neonatal brain injury is uniform and due primarily to acquired insults such as birth asphyxia is slowly being modified by epidemiologic studies.[5] The causes of neonatal brain injury are protean and are only now being revealed, owing to advances in neuroimaging and diagnostic laboratory techniques. Most neonatal brain injury is metabolic, whether from transient ischemia–reperfusion events or from defects in inherited metabolic pathways expressed soon after birth. A greater understanding of these mechanisms should provide opportunities to intervene therapeutically in both newborns and adults.

Neonatal brain injury is recognized on the basis of a unique encephalopathy that evolves from lethargy to hyperexcitability to stupor during the first three days of life.[6] Neonatal brain injury often eludes diagnosis, especially in premature infants with very low birth weight, because obvious signs are lacking or because signs that are present are attributed to developmental immaturity.[7] Clinically subtle signs and symptoms lead to a delay in the diagnosis of cerebral palsy, learning disabilities, and complex behavioral disorders until later in childhood.[8] This review will focus on the clinical investigation of basic mechanisms of neonatal brain injury and on advances in neuroimaging and developmental biology that may affect potential therapeutic interventions.

CLINICAL OBSERVATIONS

PATTERNS OF INJURY

Advanced methods of neuroimaging, such as magnetic resonance imaging (MRI), magnetic resonance spectroscopy, and diffusion-weighted MRI, have identified patterns of damage after ischemic insult to the immature brain. Such patterns depend on the severity of the insult and the age at which it occurs[9] (Fig. 1A and 1B). In addition to defining patterns of injury, neuroimaging has shown, through serial studies, that brain injury evolves over days, if not weeks.[10] This has been substantiated in animal models.[11] If time permits, various treatment interventions may be attempted as the injury evolves[12] (Fig. 2). The recognition that different regions of the brain have different susceptibility to injury at different maturational stages has led investigators to identify par-

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2004 Massachusetts Medical Society. All rights reserved.

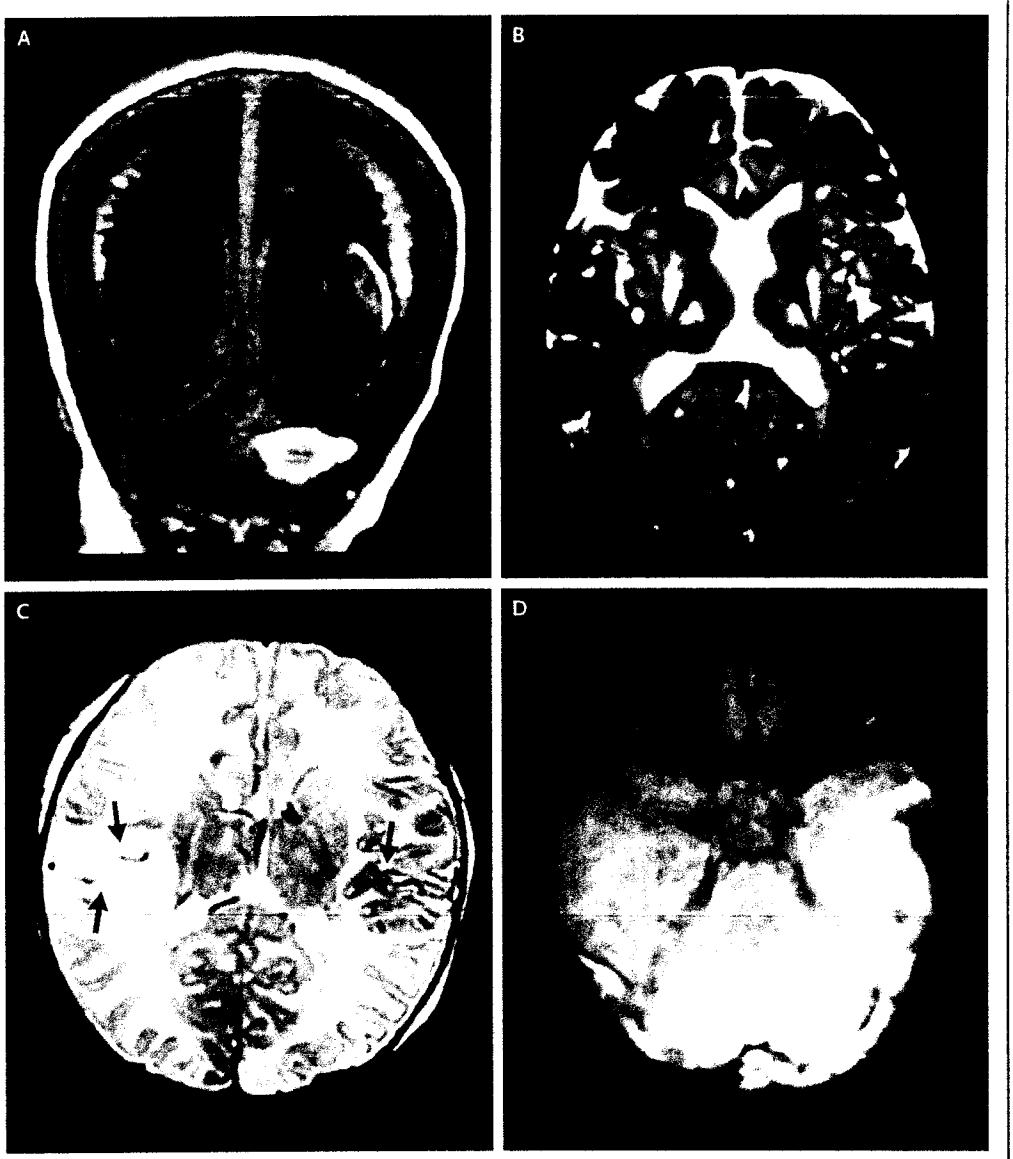

Figure 1. **Selective Regional Vulnerability Determined According to Age at Insult.**

Panel A shows an image of a neonate who was born at 24 weeks of gestation. The T_1-weighted, spin-echo MRI was performed at 28 weeks and reveals subacute white-matter injury with cystic changes and volume loss. A T_2-weighted, spin-echo image of the brain of a two-year-old child who had a documented ischemic insult at term shows chronic injury to the basal ganglia and thalamus (Panel B). A T_1-weighted image on day 2 of life revealed hyperintensity in the scarred regions shown in Panel B. In Panel C, a T_2-weighted, spin-echo image of a term newborn who presented with seizures reveals multiple acute arterial infarcts. In Panel D, a T_2-weighted, spin-echo image shows a thrombosed left transverse sinus and hemorrhagic venous infarction in a six-day-old term newborn who presented with focal seizures.

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2004 Massachusetts Medical Society. All rights reserved.

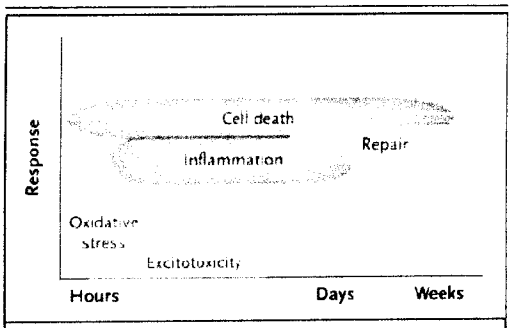

Figure 2. **Mechanisms of Brain Injury in the Term Neonate.**

Oxidative stress and excitotoxicity, through downstream intracellular signaling, produce both inflammation and repair. Cell death begins immediately and continues during a period of days to weeks. The cell-death phenotype changes from an early necrotic morphology to a pathology resembling apoptosis. This evolution is called the necrosis–apoptosis continuum.

ticular types of cells within the central nervous system that are selectively vulnerable to brain insults. Neural cells in the immature nervous system are selectively vulnerable in a way that is similar to the selectivity seen in the mature brain in patients with Parkinson's disease and those with Huntington's disease.[13]

If an ischemic insult occurs early in gestation and the baby is born prematurely, some developing oligodendrocytes and subplate neurons are lost.[14,15] Preoligodendrocytes and oligodendrocyte progenitor cells seem to be more vulnerable to ischemic injury than are mature oligodendrocytes.[16] Subplate neurons appear transiently during brain development and play a critical role in the formation of connections between the thalamus and the visual cortex.[17] In the term neonate with ischemic brain injury, however, certain neurons in the deep gray nuclei and perirolandic cortex are most likely to be injured, whereas other cells, such as neurons expressing nitric oxide synthase, seem to be resistant to ischemic injury.[18] Within the basal ganglia, neurons expressing nitric oxide synthase participate in processes of oxidative stress and excitotoxicity[14,19] that lead to the death of neighboring cells.[20]

OXIDATIVE STRESS

The neonatal brain, with its high concentrations of unsaturated fatty acids, high rate of oxygen consumption, low concentrations of antioxidants, and availability of redox-active iron, is particularly vulnerable to oxidative damage.[19] In the very immature brain, oligodendrocyte progenitor cells and preoligodendrocytes are selectively vulnerable to the depletion of antioxidants or exposure to exogenous free radicals.[21] Mature oligodendrocytes, in contrast, are highly resistant to oxidative stress, owing in part to differences in the levels of expression of antioxidant enzymes and proteins involved in programmed cell death. These characteristics of oligodendrocytes may explain why white matter often is injured selectively in the brain of the premature newborn.

EXCITOTOXICITY

Excitotoxicity refers to excessive activation of glutamatergic neurotransmission and leads to cell death.[22] Cell death due to excitotoxicity occurs in many types of cells in the newborn brain, and the initial trigger may be impairment of the uptake of glutamate by glia, resulting in overactivation of the receptors.[23] Developmental differences in the function and expression of glutamate receptors dictate the response of the newborn brain to injury. For example, oligodendrocyte progenitor cells express glutamate receptors, including α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (usually referred to as AMPA) and kainate receptors. Experimental data indicate that blockade of these receptors protects against hypoxic–ischemic injury to the white matter in the immature rodent.[24]

The production of nitric oxide by neurons that are resistant to ischemic injury depends on the coupling and activation of the *N*-methyl-D-aspartate (NMDA) receptor and, subsequently, calcium entry into the cells of the thalamus and basal ganglia.[25] When nitric oxide is produced in excessive amounts during periods of oxidative stress in these regions, it contributes to the production of free radicals.[26] However, neurons that produce nitric oxide are themselves resistant to both hypoxic–ischemic and NMDA-mediated excitotoxicity[18,27] in the immature brain; these cells become vulnerable as the brain matures. In regions where the immature NMDA receptor is expressed, such as the basal ganglia,[28] neurons that produce nitric oxide synthase are abundant. Elimination of these neurons and disruption of the postsynaptic density complex that links NMDA to these neurons result in a reduction of ischemic injury.[29] Therefore, both excitotoxicity and oxidative stress seem to mediate neonatal ischemic damage but must be understood in relation to normal development.

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2004 Massachusetts Medical Society. All rights reserved.

Case 2:08-cv-15075-PDB-SDP ECF No. 1-2, PageID.54 Filed 12/08/08 Page 37 of 51

INFLAMMATION

Maternal infection and its association with white-matter disease in the premature brain suggest other converging pathways that contribute to neonatal brain injury.[30] A population-based study that used cerebral palsy as one outcome measure for neonatal brain injury suggested that chorioamnionitis is an independent risk factor for cerebral palsy among term infants,[31] and previous studies have documented an association between chorioamnionitis and poor neurologic outcome for the preterm infant.[32]

The use of maternal infection as a marker for neonatal brain injury is problematic because of the inherent difficulty in defining chorioamnionitis. It is rare today to document chorioamnionitis by histologic examination of the placenta, and chorioamnionitis is a term that is used liberally in conditions as vague as maternal fever.[33] Nevertheless, the roles of inflammatory responses by the fetal systemic and central nervous systems seem to be critically important to understanding the genesis of brain injury in the newborn.[30] It is not known whether the inflammatory response is causal or modulatory in the cascade of events that occurs during an intrauterine or a perinatal insult to the brain.

APOPTOSIS DURING HYPOXIC–ISCHEMIC INJURY TO THE NEONATAL BRAIN

Programmed cell death, or apoptosis, is the mechanism for refining cell connections and pathways during brain development.[34] Recent data suggest that apoptosis plays a prominent role in the evolution of hypoxic–ischemic injury in the neonatal brain and may be more important than necrosis after injury.[35] During neonatal brain injury, excitotoxicity, oxidative stress, and inflammation all contribute to accelerated cell death by means of either apoptosis or necrosis, depending on the region of the brain affected and the severity of the insult.[36] Signals from cytokine death receptors, for example, result in nitric oxide–mediated necrosis when endogenous inhibitors of apoptosis are abundant[37] and in apoptosis when the inhibitors are deficient.[38] These death-receptor proteins have been documented in the brain and the cerebrospinal fluid of newborns after brain injury,[39,40] suggesting that this pathway may be a potential therapeutic target.

GENETIC EFFECTS

Similar insults to the neonatal brain will manifest themselves differently in different babies in terms of the injury, as observed on imaging studies such as MRI, and in terms of neurodevelopmental outcome. Such variability has also been observed in animal models and appears to be genetically based.[41] Certain polymorphisms may increase the risk for many complex diseases.[42,43] However, susceptibility factors for neonatal brain injury have yet to be identified clearly. Large population-based studies have indicated that biomarkers may prove useful in predicting outcome after neonatal brain injury[44,45]; similarly, population-based studies examining genetic factors may prove instructive. A recent exploratory study of very preterm infants showed an association of single-nucleotide polymorphisms such as endothelial nitric oxide synthase A(−922)G, factor VII (Arg353Gln) and del(−323)10bp-ins, and lymphotoxin α (Thr26Asn) with spastic cerebral palsy.[46]

CLINICAL SYNDROMES

NEONATAL ENCEPHALOPATHY

Neonatal encephalopathy is a major predictor of neurodevelopmental disability in term infants and occurs in 1 to 6 of every 1000 live term births.[47] The terms hypoxic–ischemic encephalopathy and birth asphyxia have been used to describe this clinical state, but many cases that are labeled neonatal encephalopathy have occurred in neonates who had neither documented hypoxia–ischemia nor asphyxia.[48] Neonatal encephalopathy is a serious condition: 15 to 20 percent of affected infants die during the newborn period, and an additional 25 percent have permanent neurologic deficits.[49]

Studies of risk factors for neonatal encephalopathy reveal that many cases are associated with antepartum risks such as maternal hypotension, infertility treatment, or thyroid disease, whereas some have both antepartum and intrapartum risk factors. Only a few cases have been associated with intrapartum risk factors such as forceps delivery, breech extraction, prolapse of the cord, abruptio placentae, or maternal fever.[5] Postnatal complications such as severe respiratory distress, sepsis, and shock occur in fewer than 10 percent of term infants with neonatal encephalopathy. Although prenatal risk factors may be present, prospective studies with the use of MRI suggest that the majority of infants with neonatal encephalopathy sustained brain injury at or near the time of birth.[9]

The severity of neonatal encephalopathy depends on both the timing and the duration of the insult. Symptoms usually evolve during a period of days, making it important to perform serial detailed

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2004 Massachusetts Medical Society. All rights reserved.

neurologic examinations.[6] In the first hours after a severe ischemic insult, neonates exhibit a depressed level of consciousness. Typically, periodic breathing with apnea or bradycardia is present, yet cranial-nerve function may be spared and intact pupillary responses and spontaneous eye movements may be present if the injury is not severe. Hypotonia with decreased movement is associated with injury to cortical regions, and seizures may occur in the most severely affected infants very soon after the insult.

A transient improvement in the level of alertness may occur during the first week of life, but this change in mental status is not accompanied by other signs of improvement in neurologic function. Refractory seizures accompanied by apneic episodes, shrill cry, and jitteriness may be seen during this period. Hypotonia and weakness in the proximal limbs, face, and bulbar musculature and exaggeration of Moro's and muscle-stretch reflexes are often observed and persist for many months. Gestational age is important in interpreting these symptoms, since premature babies have lower muscle tone than term infants and may appear abnormal if their age is not considered.

Eventually, in neonates with severe injury, respiratory arrest and other signs of brain-stem dysfunction may precede a deterioration in the level of consciousness. Scoring the clinical signs of encephalopathy (Table 1) can standardize the approach to the newborn with brain injury and help select neonates who require therapeutic intervention.[50]

NEONATAL SEIZURES

Neonatal seizures occur in patients with neonatal encephalopathy and may be a sign of reversible metabolic disorders, structural injury, or malformations. Seizures can be manifested subtly as ocular movements such as horizontal tonic deviation of the eyes or sustained eye opening or blinking, orolingual movements such as tongue or lip smacking or sucking, rowing or bicycling movements of the extremities, or recurrent apnea. Focal clonic seizures are seen often in patients with arterial or venous infarction. The development of bedside monitoring devices such as the amplitude-integrated electroencephalograph (cortical-function monitor)[51] permits nurses and neonatology personnel to assess brain-wave activity. Although cortical-function monitoring can help evaluate newborns for seizures, brain-wave activity should be validated with standard electroencephalography.[51,52]

Neonatal seizures may result from metabolic disorders such as a congenital deficiency of sulfite oxidase, and the use of MRI can help distinguish these seizures from those due to hypoxic–ischemic events and other forms of metabolic or genetic disease.[53,54] In conjunction with laboratory testing, MRI also provides information regarding traumatic and infectious causes. Skull fractures, occurring during delivery or as a result of blunt trauma to the maternal abdomen, can be associated with underlying cortical damage. Reversible causes of seizures such as hypoglycemia, hypocalcemia, hyponatremia, hypoxemia, acidosis, and hyperbilirubinemia are often part of an underlying disorder (Table 2). Lumbar puncture has reemerged as a major tool for diagnosing certain genetic disorders, such as pediatric neurotransmitter diseases (diseases involving inborn errors of metabolism that affect the central nervous system in children) and glucose-transporter defects.[55]

Neonatal seizures do not always imply poor neurodevelopmental outcome, although they are difficult to treat effectively.[56] It is unclear how aggressively neonatal seizures should be treated, or for how long and with what medications. The development of anticonvulsant drugs has not been directed toward the treatment of neonatal seizures, even though most seizures begin in the first year of life.[1] Therefore, drug therapy for the newborn is empirical and based on limited data. Most pediatric neurologists are reluctant to prescribe continuous anticonvulsant therapy for newborns after symptoms of brain injury have resolved or the underlying disease process has been identified and treated. Clinical trials are needed in this area.

NEONATAL STROKE

Many affected newborns appear healthy in the immediate newborn period and, because they may not have clinical signs of stroke, the diagnosis is made

Table 1. Encephalopathy Score.

Variable	Score=0	Score=1
Feeding	Normal	Gavage, gastrostomy tube, or does not tolerate oral feeding
Alertness	Alert	Irritable, poorly responsive, or comatose
Muscle tone	Normal	Hypotonia or hypertonia
Respiratory status	Normal	Respiratory distress (need for continuous positive airway pressure or mechanical ventilation)
Reflexes	Normal	Hyperreflexia, hyporeflexia, or absent reflexes
Seizure	None	Suspected or confirmed clinical seizure

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2004 Massachusetts Medical Society. All rights reserved.

Table 2. **Differential Diagnosis of Neonatal Seizures by Day of Presentation.**

Day 1
Traumatic brain injury (subdural, subarachnoid, or intraparenchymal hemorrhages)*
Hypoxia and ischemia
Stroke (arterial more likely than venous)
Infection (bacterial or viral)*
Severe inborn metabolic disorder (e.g., deficiency of sulfite oxidase or nonketotic hyperglycinemia)*
Systemic hypoglycemia*
Electrolyte disturbance (hypocalcemia or hyponatremia)*
Intoxication (maternal substance abuse)*
Day 2
Stroke (especially venous thrombosis)
Traumatic brain injury*
Inborn metabolic disorder (especially glucose-transporter defect)*
Day 3
Partial defect in metabolism (e.g., organic acidemias or aminoacidopathies)*
Benign neonatal convulsions
Stroke (either arterial or venous)
Withdrawal (from maternal substance abuse)*
Traumatic brain injury*
Inborn metabolic disorder*

* This disorder requires medical or surgical intervention.

only retrospectively.[57] Neonatal strokes are often arterial in origin and ischemic in nature, although at least 30 percent are due to sinovenous thrombosis.[58] Recent attempts to identify risk factors with the use of population-based studies have implicated prepartum factors such as preeclampsia and intrauterine growth restriction.[48] Coagulation abnormalities (decreased levels of protein C, protein S, and antithrombin III and elevated plasma levels of Lp(a) lipoprotein and homocysteine) as well as certain genetic mutations and polymorphisms (including factor V Leiden G1691A, factor II G20210A, and methylenetetrahydrofolate reductase C677T) have been identified as risk factors,[59,60] especially in neonates with stroke due to cerebral venous thrombosis. Newborns with stroke usually have more than one risk factor,[61,62] and perinatal complications such as hypoxic–ischemic events are frequently present.

In newborns presenting with neonatal encephalopathy and stroke, MRI will help document the type of stroke, and testing for prothrombotic disorders may improve diagnostic yield[63] (Fig. 1C and 1D). The risk of recurrence of neonatal stroke is low (less than 5 percent) and seems to be associated with intercurrent illnesses or complications of systemic disorders such as congenital heart disease. However, children in whom recurrent thromboembolism develops may have coagulation factor defects.[64]

Intraventricular hemorrhage, which occurs commonly in very premature newborns, should not be confused with fetal hemorrhagic stroke, which occurs between 14 weeks of gestation and the onset of labor.[65] Intraventricular hemorrhage, unlike stroke, is not associated with poor neurodevelopmental outcome unless there is evidence of parenchymal brain injury.[66]

Patterns of brain injury seen on MRI and subsequently on clinical examination are strongly influenced by the gestational age of the newborn at the time of the stroke.[67] Although most strokes occur at or near the time of birth, resulting in hemiplegic cerebral palsy, some that are diagnosed later in a child's life have more subtle findings on examination (e.g., mild dystonia and cognitive disabilities), and MRI is unable to document precisely the time of the insult.

SUBTLE NEONATAL SYNDROMES

Although subtle brain-injury syndromes, such as subclinical neonatal stroke, may take months to identify, screening procedures have improved the diagnostic yield. These screening procedures include ultrasonographic examination of the head and cortical-function monitoring. MRI has been the definitive test for identifying both abnormalities in the periventricular white matter and loss of brain volume, but many hospitals do not yet have MRI facilities for evaluating sick newborns. MRI-compatible incubators have been developed for transporting sick newborns, but they are expensive and their availability is limited.[68,69]

INSIGHTS FROM NEUROIMAGING

Patterns of brain injury are emerging with the use of MRI, and regional changes seen on MRI are predictive of particular neurodevelopmental syndromes later in childhood.[70,71] High-quality MRI has expanded the differential diagnoses of neonatal encephalopathy, which was previously limited to histopathological conditions such as periventricular leukomalacia, kernicterus, and very large cortical malformations. Since myelination is still occurring in the neonatal brain, and since the water content of the neonatal brain is greater than that of the mature brain, injury has a different appearance and

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2004 Massachusetts Medical Society. All rights reserved.

time course in the neonatal brain than in the adult brain.[9,70-72] Since the posterior limb of the internal capsule is the first area to myelinate in the immature brain, loss of signal on T_1-weighted spin-echo MRI in this region is a reliable indicator of severe hypoxic–ischemic injury.[71]

In a study of 104 children with evidence of bilateral hypoxic–ischemic brain damage, at least three different patterns were observed with the use of MRI.[73] Periventricular leukomalacia was observed in premature infants with a history of subacute or chronic hypoxia and ischemia. Lesions in the basal ganglia and thalamus occurred in full-term babies who had profound asphyxia. Multicystic changes were seen in a minority of infants who had severe encephalopathy but only a mild hypoxic–ischemic event; this group may include babies who had underlying fetal infections or metabolic disorders that had eluded diagnosis. These data suggest that injury is related to the gestational age at the time of the insult, although the severity or chronicity of the insult may be a better indicator of eventual outcome.

In a study of 351 term infants presenting with neonatal encephalopathy or seizures documented by either MRI of the brain or postmortem histopathological procedures, most showed evidence of injury acquired at or near the time of birth. The timing of the lesion, however, does not exclude the possibility of genetic or antenatally acquired risk factors.[9]

Diffusion-weighted MRI of the neonate can identify early injury after an insult[74] owing to its ability to detect subtle alterations in brain water. Simple diffusion-weighted MRI can detect, but may often overestimate, areas of cytotoxic edema, in which cystic changes may gradually develop.[75] Diffusion tensor imaging is a technique that permits observation of molecular diffusion of water and microstructural organization, particularly the myelination of fibers in the white matter, and early detection of small injuries or abnormalities.[76] Serial diffusion tensor imaging can detect differences in the maturation of white matter in infants with or without injury and can provide detailed and quantifiable data regarding brain development in injured newborns.[77]

Magnetic resonance spectroscopy, especially three-dimensional magnetic resonance spectroscopy of the neonatal brain, can detect metabolites such as lactate, *N*-acetyl aspartate, choline, and creatine that provide functional data regarding metabolic integrity in specific regions of the brain[78] (Fig. 3). These techniques can be used to define the injury at its inception and can potentially be linked to future neurodevelopmental outcome measures to determine which neonates are at high risk for adverse neurologic sequelae[79] and should receive therapy. The combination of clinical signs of neonatal encephalopathy (Table 1) and patterns of injury seen with various MRI techniques may improve selection.[80,81]

INTERVENTIONS

It is very difficult to predict during the neonatal period which neonates will suffer the most profound damage after an insult to the central nervous system, since more than 30 percent of neonates presenting with moderate encephalopathy have normal outcomes.[49] Preliminary results of two randomized clinical trials of either systemic cooling or selective head cooling in encephalopathic neonates[82,83] suggest that moderate hypothermia is safe in the high-risk newborn.[84] In at least one study, newborns with moderate encephalopathy had better neurodevelopmental outcomes at 18 months than did newborns in the normothermic group.[82] Neonates with congenital heart disease seem to be vulnerable to white-matter injury during surgical correction of their cardiac defects,[85] and the clinical use of hypothermia for these infants suggests that hypothermia is safe and can be beneficial.[86] However, the therapeutic window for the use of hypothermia has yet to be defined.

Studies in laboratory animals have shown that the immature brain responds differently to treatment than does the mature brain. Therapy designed to ameliorate brain injury in adults may worsen outcomes in neonates, possibly by accentuating apoptosis. Drugs that block NMDA receptors or potentiate γ-aminobutyric acid type A receptors can trigger widespread apoptosis in the developing brain of rodents.[87] Indeed, drugs that act at these sites, such as midazolam, nitrous oxide, and isoflurane, and that are commonly used for analgesia in the human neonate also produce persistent learning impairments when administered to seven-day-old rats.[88] However, drugs such as allopurinol, deferoxamine, and 3-iminobiotin, when given soon after the insult, interrupt injuries caused by free radicals and have shown benefit in large-animal models.[89-91] The neuroprotective effect of exogenously administered erythropoietin has received much attention for ischemic disease, and promising

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2004 Massachusetts Medical Society. All rights reserved.

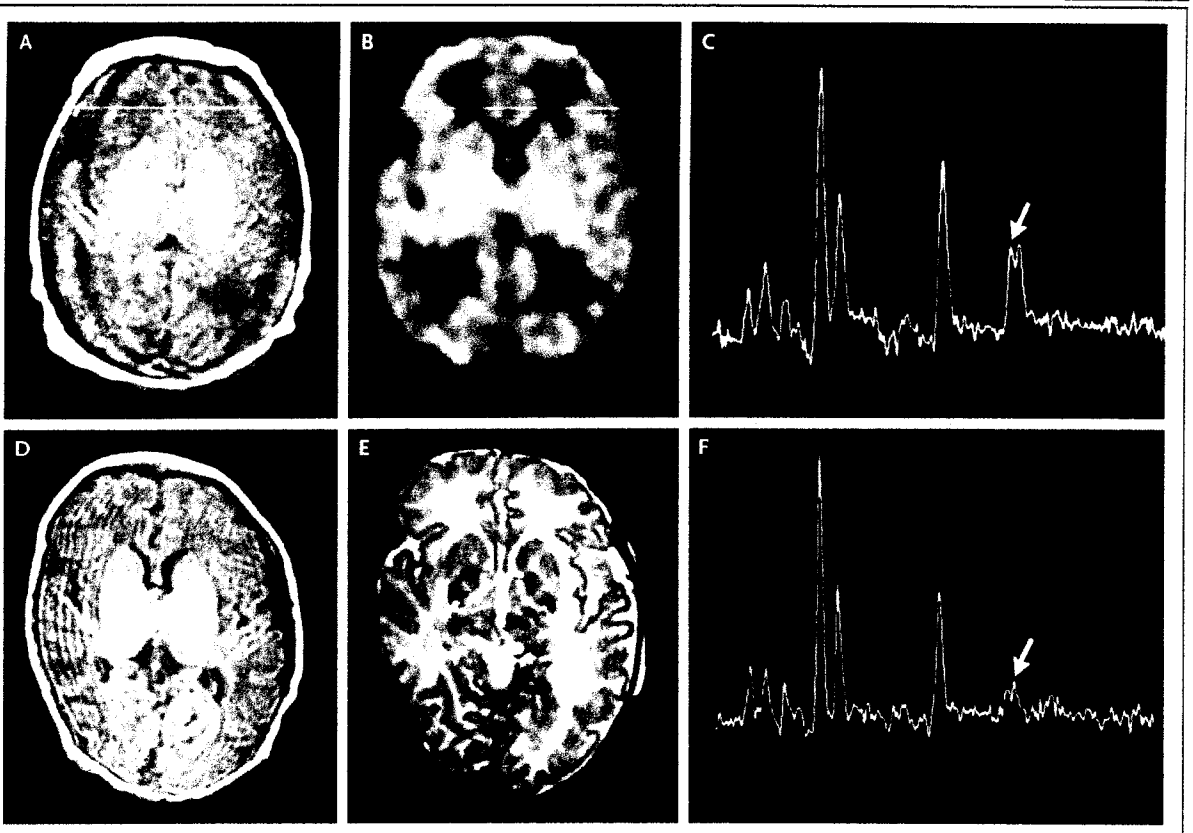

Figure 3. **Evolution of Brain Injury as Seen with MRI.**

A normal structural image (Panel A), a diffusion-weighted MRI (Panel B), and lactate accumulation in the basal ganglia on magnetic resonance spectroscopy (Panel C, arrow) are shown in the same newborn at 1 day of life. At day 8, T_1-weighted MRI (Panel D) and T_2-weighted MRI (Panel E) reveal extensive damage to the deep gray nuclei, and magnetic resonance spectroscopy shows diminution of the lactate peak (Panel F, arrow).

data are emerging for the newborn.[92] Judiciously choosing various methods of treatment aimed at particular phases of the injury cascade (Fig. 2) may enhance protection or repair. The administration of growth factors, such as erythropoietin or brain-derived neurotrophic factor, throughout or even late in the injury process, might enhance repair. Recent data show that combination therapy with hypothermia and topiramate to block excitotoxicity improves outcome in a rodent model.[93] The search for whom to treat and the best therapy is ongoing. Meanwhile, the standards of care in the neonatal intensive care unit continue to affect the evolution of brain injury.[94] No longer is hypocapnia or hypoxemia induced in sick newborns to treat respiratory distress, and reduction in the use of mechanical ventilation has been associated with a decreasing incidence of cystic periventricular leukomalacia during the past decade.[95] Attention to drug use and careful identification and management of neonatal seizures might improve outcome even if there are severe underlying metabolic disorders. However, careful management strategies that take into account the age of the newborn brain and its inherent susceptibility to oxidative stress and programmed cell death in combination with pharmacologic therapies may optimally protect the brain.

Prevalence data suggest that 8000 babies are born each year in the United States with cerebral palsy, which is only one outcome of neonatal brain injury.[96] Since improved management in the first decade of life has led to survival into adulthood, current medical practice should incorporate plans for care that include the management of seizures

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2004 Massachusetts Medical Society. All rights reserved.

Case 2:08-cv-15075-PDB-SDP ECF No. 1-2, PageID.59 Filed 12/08/08 Page 42 of 51

and spasticity as well as cognitive and behavioral assessments that will improve the quality of life.

SUMMARY

A reasoned approach to the newborn with brain injury is emerging from both clinical and laboratory data that have been accumulating during the past decade. Early recognition of at-risk newborns by means of advanced methods of neuroimaging, combined with a plan for rational intervention, may result in the prevention or the reduction in the incidence of lifelong disabilities such as cerebral palsy, epilepsy, and behavioral and learning disorders.

Dr. Ferriero reports having received a consulting fee and grant support from Johnson & Johnson.

I am indebted to Drs. Steven P. Miller, Yvonne W. Wu, and Thomas A. Rando for helpful suggestions with the manuscript; to Dr. Faye Silverstein for manuscript development; to Dr. A. James Barkovich for magnetic resonance images; and to Kei Kaneshiro for assistance in the preparation of the manuscript.

REFERENCES

1. Maytal J, Shinnar S, Moshe SL, Alvarez LA. Low morbidity and mortality of status epilepticus in children. Pediatrics 1989;83:323-31.
2. Fullerton HJ, Chetkovich DM, Wu YW, Smith WS, Johnston SC. Deaths from stroke in US children, 1979 to 1998. Neurology 2002;59:34-9.
3. Nelson KB, Lynch JK. Stroke in newborn infants. Lancet Neurol 2004;3:150-8.
4. Barker DJ. Fetal origins of cardiovascular disease. Ann Med 1999;31:Suppl 1:3-6.
5. Badawi N, Kurinczuk JJ, Keogh JM, et al. Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. BMJ 1998;317:1554-8.
6. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. Arch Neurol 1976;33:696-705.
7. Mercuri E, Guzzetta A, Laroche S, et al. Neurologic examination of preterm infants at term age: comparison with term infants. J Pediatr 2003;142:647-55.
8. Mercuri E, Anker S, Guzzetta A, et al. Visual function at school age in children with neonatal encephalopathy and low Apgar scores. Arch Dis Child Fetal Neonatal Ed 2004;89:F258-F262.
9. Cowan F, Rutherford M, Groenendaal F, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. Lancet 2003;361:736-42.
10. McKinstry RC, Miller JH, Snyder AZ, et al. A prospective, longitudinal diffusion tensor imaging study of brain injury in newborns. Neurology 2002;59:824-33.
11. Nakajima W, Ishida A, Lange MS, et al. Apoptosis has a prolonged role in the neurodegeneration after hypoxic ischemia in the newborn rat. J Neurosci 2000;20:7994-8004.
12. Ferriero DM. Timing is everything — delaying therapy for delayed cell death. Dev Neurosci 2002;24:349-51.
13. McQuillen PS, Ferriero DM. Selective vulnerability in the developing central nervous system. Pediatr Neurol 2004;30:227-35.
14. Back SA, Luo NL, Borenstein NS, Levine JM, Volpe JJ, Kinney HC. Late oligodendrocyte progenitors coincide with the developmental window of vulnerability for human perinatal white matter injury. J Neurosci 2001;21:1302-12.
15. McQuillen PS, Sheldon RA, Shatz CJ, Ferriero DM. Selective vulnerability of subplate neurons after early neonatal hypoxia-ischemia. J Neurosci 2003;23:3308-15.
16. Haynes RL, Folkerth RD, Keefe RJ, et al. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. J Neuropathol Exp Neurol 2003;62:441-50.
17. Kanold PO, Kara P, Reid RC, Shatz CJ. Role of subplate neurons in functional maturation of visual cortical columns. Science 2003;301:521-5.
18. Ferriero DM, Arcavi LJ, Sagar SM, McIntosh TK, Simon RP. Selective sparing of NADPH-diaphorase neurons in neonatal hypoxia-ischemia. Ann Neurol 1988;24:670-6.
19. Halliwell B. Reactive oxygen species and the central nervous system. J Neurochem 1992;59:1609-23.
20. Ferriero DM, Holtzman DM, Black SM, Sheldon RA. Neonatal mice lacking neuronal nitric oxide synthase are less vulnerable to hypoxic-ischemic injury. Neurobiol Dis 1996;3:64-71.
21. Baud O, Greene AE, Li J, Wang H, Volpe JJ, Rosenberg PA. Glutathione peroxidase-catalase cooperativity is required for resistance to hydrogen peroxide by mature rat oligodendrocytes. J Neurosci 2004;24:1531-40.
22. Olney JW. Excitotoxicity, apoptosis and neuropsychiatric disorders. Curr Opin Pharmacol 2003;3:101-9.
23. McDonald JW, Johnston MV. Physiological and pathophysiological roles of excitatory amino acids during central nervous system development. Brain Res Brain Res Rev 1990;15:41-70.
24. Deng W, Wang H, Rosenberg PA, Volpe JJ, Jensen FE. Role of metabotropic glutamate receptors in oligodendrocyte excitotoxicity and oxidative stress. Proc Natl Acad Sci U S A 2004;101:7751-6.
25. Ferriero DM, Ashwal S. Effects of nitric oxide on neuronal and cerebrovascular function. In: Donn SM, Sinha SK, Chiswick ML, eds. Birth asphyxia and the brain: basic science and clinical implications. Armonk, N.Y.: Futura Publishing, 2002:153-88.
26. Beckman JS, Viera L, Estevez AG, Teng R. Nitric oxide and peroxynitrite in the perinatal period. Semin Perinatol 2000;24:37-41.
27. Ferriero DM, Arcavi LJ, Simon RP. Ontogeny of excitotoxic injury to nicotinamide adenine dinucleotide phosphate diaphorase reactive neurons in the neonatal rat striatum. Neuroscience 1990;36:417-24.
28. Black SM, Bedolli MA, Martinez S, Bristow JD, Ferriero DM, Soifer SJ. Expression of neuronal nitric oxide synthase corresponds to regions of selective vulnerability to hypoxia-ischaemia in the developing rat brain. Neurobiol Dis 1995;2:145-55.
29. Aarts MM, Tymianski M. Novel treatment of excitotoxicity: targeted disruption of intracellular signalling from glutamate receptors. Biochem Pharmacol 2003;66:877-86.
30. Dammann O, Kuban KC, Leviton A. Perinatal infection, fetal inflammatory response, white matter damage, and cognitive limitations in children born preterm. Ment Retard Dev Disabil Res Rev 2002;8:46-50.
31. Wu YW, Escobar GJ, Grether JK, Croen LA, Greene JD, Newman TB. Chorioamnionitis and cerebral palsy in term and near-term infants. JAMA 2003;290:2677-84.
32. Wu YW, Colford JM Jr. Chorioamnionitis as a risk factor for cerebral palsy: a meta-analysis. JAMA 2000;284:1417-24.
33. Khong TY, Bendon RW, Qureshi F, et al. Chronic deciduitis in the placental basal plate: definition and interobserver reliability. Hum Pathol 2000;31:292-5.
34. Blaschke AJ, Staley K, Chun J. Widespread programmed cell death in proliferative and postmitotic regions of the fetal cerebral cortex. Development 1996;122:1165-74.
35. Hu BR, Liu CL, Ouyang Y, Blomgren K, Siesjö BK. Involvement of caspase-3 in cell death after hypoxia-ischemia declines during brain maturation. J Cereb Blood Flow Metab 2000;20:1294-300.
36. Martin LJ, Al-Abdulla NA, Brambrink AM, Kirsch JR, Sieber FE, Portera-Cailliau C. Neurodegeneration in excitotoxicity, global cerebral ischemia, and target deprivation: a perspective on the contributions of apo-

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2004 Massachusetts Medical Society. All rights reserved.

ptosis and necrosis. Brain Res Bull 1998;46:281-309.
37. Raoul C, Estevez AG, Nishimune H, et al. Motoneuron death triggered by a specific pathway downstream of Fas: potentiation by ALS-linked SOD1 mutations. Neuron 2002;35:1067-83.
38. Graham EM, Sheldon RA, Flock DL, et al. Neonatal mice lacking functional Fas death receptors are resistant to hypoxic-ischemic brain injury. Neurobiol Dis 2004;17:89-98.
39. van Landeghem FK, Felderhoff-Mueser U, Moysich A, et al. Fas (CD95/Apo-1)/Fas ligand expression in neonates with pontosubicular neuron necrosis. Pediatr Res 2002;51:129-35.
40. Felderhoff-Mueser U, Buhrer C, Groneck P, Obladen M, Bartmann P, Heep A. Soluble Fas (CD95/Apo-1), soluble Fas ligand, and activated caspase 3 in the cerebrospinal fluid of infants with posthemorrhagic and nonhemorrhagic hydrocephalus. Pediatr Res 2003;54:659-64.
41. Sheldon RA, Sedik C, Ferriero DM. Strain-related brain injury in neonatal mice subjected to hypoxia-ischemia. Brain Res 1998;810:114-22.
42. Hoppe C, Klitz W, Cheng S, et al. Gene interactions and stroke risk in children with sickle cell anemia. Blood 2004;103:2391-6.
43. Davey Smith G, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol 2003;32:1-22.
44. Kaukola T, Satyaraj E, Patel DD, et al. Cerebral palsy is characterized by protein mediators in cord serum. Ann Neurol 2004;55:186-94.
45. Nelson KB, Dambrosia JM, Grether JK, Phillips TM. Neonatal cytokines and coagulation factors in children with cerebral palsy. Ann Neurol 1998;44:665-75.
46. Nelson KB, Dambrosia JM, Iovannisci DM, Cheng S, Grether JK, Lammer E. Genetic polymorphisms and cerebral palsy in very preterm infants. Pediatr Res (in press).
47. Neonatal encephalopathy and cerebral palsy: defining the pathogenesis and pathophysiology. Washington, D.C.: American College of Obstetricians and Gynecologists, 2003.
48. Wu YW, March WM, Croen LA, et al. Perinatal stroke in children with motor impairment: a population-based study. Pediatrics 2004;114:612-9.
49. Volpe JJ. Neurology of the newborn. 4th ed. Philadelphia: W.B. Saunders, 2001:912.
50. Miller SP, Latal B, Clark H, et al. Clinical signs predict 30-month neurodevelopmental outcome after neonatal encephalopathy. Am J Obstet Gynecol 2004;190:93-9.
51. Toet MC, van der Meij W, de Vries LS, Uiterwaal CS, van Huffelen KC. Comparison between simultaneously recorded amplitude integrated electroencephalogram (cerebral function monitor) and standard electroencephalogram in neonates. Pediatrics 2002;109:772-9.
52. Rennie JM, Chorley G, Boylan GB, Pressler R, Nguyen Y, Hooper R. Non-expert use of the cerebral function monitor for neonatal seizure detection. Arch Dis Child Fetal Neonatal Ed 2004;89:F37-F40.
53. Barkovich AJ. The encephalopathic neonate: choosing the proper imaging technique. AJNR Am J Neuroradiol 1997;18:1816-20.
54. *Idem*. Magnetic resonance imaging: role in the understanding of cerebral malformations. Brain Dev 2002;24:2-12.
55. Hyland K. The lumbar puncture for diagnosis of pediatric neurotransmitter diseases. Ann Neurol 2003;54:Suppl 6:S13-S17.
56. Painter MJ, Scher MS, Stein AD, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med 1999;341:485-9.
57. Golomb MR, MacGregor DL, Domi T, et al. Presumed pre- or perinatal arterial ischemic stroke: risk factors and outcomes. Ann Neurol 2001;50:163-8.
58. deVeber G, Andrew M, Adams C, et al. Cerebral sinovenous thrombosis in children. N Engl J Med 2001;345:417-23.
59. Gunther G, Junker R, Strater R, et al. Symptomatic ischemic stroke in full-term neonates: role of acquired and genetic prothrombotic risk factors. Stroke 2000;31:2437-41. [Erratum, Stroke 2001;32:279.]
60. Mercuri E, Cowan F, Gupte G, et al. Prothrombotic disorders and abnormal neurodevelopmental outcome in infants with neonatal cerebral infarction. Pediatrics 2001;107:1400-4.
61. Heller C, Heinecke A, Junker R, et al. Cerebral venous thrombosis in children: a multifactorial origin. Circulation 2003;108:1362-7.
62. Wu YW, Hamrick SE, Miller SP, et al. Intraventricular hemorrhage in term neonates caused by sinovenous thrombosis. Ann Neurol 2003;54:123-6.
63. deVeber G. Arterial ischemic strokes in infants and children: an overview of current approaches. Semin Thromb Hemost 2003;29:567-73.
64. Kurnik K, Kosch A, Strater R, Schobess R, Heller C, Nowak-Gottl U. Recurrent thromboembolism in infants and children suffering from symptomatic neonatal arterial stroke: a prospective follow-up study. Stroke 2003;34:2887-92.
65. Ozduman K, Pober BR, Barnes P, et al. Fetal stroke. Pediatr Neurol 2004;30:151-62.
66. Vohr BR, Allan WC, Westerveld M, et al. School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. Pediatrics 2003;111:e340-6.
67. Takanashi J, Barkovich AJ, Ferriero DM, Suzuki H, Kohno Y. Widening spectrum of congenital hemiplegia: periventricular venous infarction in term neonates. Neurology 2003;61:531-3.
68. Dumoulin CL, Rohling KW, Piel JE, et al. Magnetic resonance imaging compatible neonate incubator. Magn Reson Engineering 2002;15:117-28.
69. Erberich SG, Friedlich P, Seri I, Nelson MD Jr, Bluml S. Functional MRI in neonates using neonatal head coil and MR compatible incubator. Neuroimage 2003;20:683-92.
70. Barnett A, Mercuri E, Rutherford M, et al. Neurological and perceptual-motor outcome at 5-6 years of age in children with neonatal encephalopathy: relationship with neonatal brain MRI. Neuropediatrics 2002;33:242-8.
71. Rutherford MA, Pennock JM, Counsell SJ, et al. Abnormal magnetic resonance signal in the internal capsule predicts poor neurodevelopmental outcome in infants with hypoxic-ischemic encephalopathy. Pediatrics 1998;102:323-8.
72. Roland EH, Poskitt K, Rodriguez E, Lupton BA, Hill A. Perinatal hypoxic-ischemic thalamic injury: clinical features and neuroimaging. Ann Neurol 1998;44:161-6.
73. Sie LT, van der Knaap MS, Oosting J, de Vries LS, Lafeber HN, Valk J. MR patterns of hypoxic-ischemic brain damage after prenatal, perinatal or postnatal asphyxia. Neuropediatrics 2000;31:128-36.
74. Westmark KD, Barkovich AJ, Sola A, Ferriero D, Partridge JC. Patterns and implications of MR contrast enhancement in perinatal asphyxia: a preliminary report. AJNR Am J Neuroradiol 1995;16:685-92.
75. Roelants-van Rijn AM, Nikkels PG, Groenendaal F, et al. Neonatal diffusion-weighted MR imaging: relation with histopathology or follow-up MR examination. Neuropediatrics 2001;32:286-94.
76. Partridge SC, Mukherjee P, Henry R, et al. Diffusion tensor imaging: serial quantitation of white matter tract maturity in premature newborns. Neuroimage 2004;22:1302-14.
77. Miller SP, Vigneron DB, Henry RG, et al. Serial quantitative diffusion tensor MRI of the premature brain: development in newborns with and without injury. J Magn Reson Imaging 2002;16:621-32.
78. Vigneron DB, Barkovich AJ, Noworolski SM, et al. Three-dimensional proton MR spectroscopy imaging of premature and term neonates. AJNR Am J Neuroradiol 2001;22:1424-33.
79. Miller SP, Newton N, Ferriero DM, et al. MRS predictors of 30-month outcome following perinatal depression: role of proton MRS and socioeconomic factors. Pediatr Res 2002;52:71-7.
80. Kadri M, Shu S, Holshouser B, et al. Proton magnetic resonance spectroscopy improves outcome prediction in perinatal CNS insults. J Perinatol 2003;23:181-5.
81. Kaufman SA, Miller SP, Ferriero DM,

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2004 Massachusetts Medical Society. All rights reserved.

Glidden DH, Barkovich AJ, Partridge JC. Encephalopathy as a predictor of magnetic resonance imaging abnormalities in asphyxiated newborns. Pediatr Neurol 2003;28:342-6.

82. Gluckman PD, Wyatt JS, Azzopardi RB, et al. Selective head cooling with mild systemic hypothermia to improve neurodevelopmental outcome following neonatal encephalopathy: the CoolCap Study. Pediatr Res 2004;55:Suppl:582A. abstract.

83. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Safety of whole body hypothermia for hypoxic-ischemic encephalopathy (HIE). Pediatr Res 2004;55:Suppl:582A. abstract.

84. Feigin V, Anderson N, Gunn A, Rodgers A, Anderson C. The emerging role of therapeutic hypothermia in acute stroke. Lancet Neurol 2003;2:529.

85. Miller SP, McQuillen PS, Vigneron DB, et al. Preoperative brain injury in newborns with transposition of the great arteries. Ann Thorac Surg 2004;77:1698-706.

86. Bellinger DC, Jonas RA, Rappaport LA, et al. Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. N Engl J Med 1995; 332:549-55.

87. Ikonomidou C, Bosch F, Miksa M, et al. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science 1999;283:70-4.

88. Jevtovic-Todorovic V, Hartman RE, Izumi Y, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci 2003; 23:876-82.

89. Sarco D, Becker J, Palmer C, Sheldon RA, Ferriero DM. The neuroprotective effect of deferoxamine in the hypoxic-ischemic immature mouse brain. Neurosci Lett 2000; 282:113-6.

90. Peeters-Scholte C, Braun K, Koster J, et al. Effects of allopurinol and deferoxamine on reperfusion injury of the brain in newborn piglets after neonatal hypoxia-ischemia. Pediatr Res 2003;54:516-22.

91. Peeters-Scholte C, Koster J, Veldhuis W, et al. Neuroprotection by selective nitric oxide synthase inhibition at 24 hours after perinatal hypoxia-ischemia. Stroke 2002; 33:2304-10.

92. Juul SE. Nonerythropoietic roles of erythropoietin in the fetus and neonate. Clin Perinatol 2000;27:527-41.

93. Liu Y, Barks JD, Xu G, Silverstein FS. Topiramate extends the therapeutic window for hypothermia-mediated neuroprotection after stroke in neonatal rats. Stroke 2004; 35:1460-5.

94. Gressens P, Rogido M, Paindaveine B, Sola A. The impact of neonatal intensive care practices on the developing brain. J Pediatr 2002;140:646-53.

95. Hamrick SE, Miller SP, Leonard C, et al. Trends in severe brain injury and neurodevelopmental outcome in premature newborns: the role of cystic periventricular leukomalacia. J Pediatr (in press).

96. Winter S, Autry A, Boyle C, Yeargin-Allsopp M. Trends in the prevalence of cerebral palsy in a population-based study. Pediatrics 2002;110:1220-5.

Copyright © 2004 Massachusetts Medical Society.

ELECTRONIC ACCESS TO THE *JOURNAL'S* CUMULATIVE INDEX

At the *Journal's* site on the World Wide Web (**www.nejm.org**), you can search an index of all articles published since January 1975 (abstracts 1975–1992, full text 1993–present). You can search by author, key word, title, type of article, and date. The results will include the citations for the articles plus links to the full text of articles published since 1993. For nonsubscribers, time-limited access to single articles and 24-hour site access can also be ordered for a fee through the Internet (**www.nejm.org**).

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2004 Massachusetts Medical Society. All rights reserved.

CEREBRAL SINOVENOUS THROMBOSIS IN CHILDREN

GABRIELLE DEVEBER, M.D., MAUREEN ANDREW, M.D., COLEEN ADAMS, M.B., BRUCE BJORNSON, M.D., FRANCES BOOTH, M.D., DAVID J. BUCKLEY, M.B., CH.B., CAROL S. CAMFIELD, M.D., MICHÈLE DAVID, M.D., PETER HUMPHREYS, M.D., PIERRE LANGEVIN, M.D., E. ATHEN MACDONALD, M.D., AND JANE GILLETT, M.D., FOR THE CANADIAN PEDIATRIC ISCHEMIC STROKE STUDY GROUP*

ABSTRACT

Background Cerebral sinovenous thrombosis in children is a serious disorder, and information is needed about its prevention and treatment.

Methods The Canadian Pediatric Ischemic Stroke Registry was initiated in 1992 at the 16 pediatric tertiary care centers in Canada. Children (newborn to 18 years of age) with symptoms and radiographic confirmation of sinovenous thrombosis were included.

Results During the first six years of the registry, 160 consecutive children with sinovenous thrombosis were enrolled, and the incidence of the disorder was 0.67 case per 100,000 children per year. Neonates were most commonly affected. Fifty-eight percent of the children had seizures, 76 percent had diffuse neurologic signs, and 42 percent had focal neurologic signs. Risk factors included head and neck disorders (in 29 percent), acute systemic illnesses (in 54 percent), chronic systemic diseases (in 36 percent), and prothrombotic states (in 41 percent). Venous infarcts occurred in 41 percent of the children. Fifty-three percent of the children received antithrombotic agents. Neurologic deficits were present in 38 percent of the children, and 8 percent died; half the deaths were due to sinovenous thrombosis. Predictors of adverse neurologic outcomes were seizures at presentation and venous infarcts.

Conclusions Sinovenous thrombosis in children affects primarily neonates and results in neurologic impairment or death in approximately half the cases. The occurrence of venous infarcts or seizures portends a poor outcome. (N Engl J Med 2001;345:417-23.)

Copyright © 2001 Massachusetts Medical Society.

CEREBRAL sinovenous thrombosis in children is a rare disorder but one that is increasingly diagnosed because of greater clinical awareness, sensitive neuroimaging techniques, and the survival of children with previously lethal diseases that confer a predisposition to sinovenous thrombosis.[1-3] The literature on sinovenous thrombosis in children consists only of case reports and analyses of small case series.[4-10] Extrapolating the results of studies of adults to children is of limited value because of large age-related differences in the hemostatic, vascular, and neurologic systems. An understanding of the epidemiology of sinovenous thrombosis in children is necessary to define critical clinical settings and develop interventional strategies. The Canadian Pediatric Ischemic Stroke Registry was established to obtain comprehensive prospective epidemiologic data on stroke, including sinovenous thrombosis, in children.

METHODS

Patients

All 16 pediatric tertiary care centers in Canada participated in the registry. Children from birth (with a gestational age of more than 36 weeks) to 18 years of age were eligible for the study if they had radiologically confirmed sinovenous thrombosis. The children were classified as neonates (less than 1 month old) or nonneonates (1 month to 18 years old). A neurologist at each center maintained a prospective list of consecutive children with objectively diagnosed sinovenous thrombosis. A research nurse visited each center at regular intervals, checked the completeness of patient identification by searching the medical-records data base for discharge diagnoses, with the use of the *International Classification of Diseases, Ninth Revision* (ICD-9) codes for sinovenous thrombosis (437.6 and 325),[11] and filled out standardized data-collection forms. The data were entered into a central data base, reviewed for inaccuracies, missing data, and inconsistencies, and corrected according to a review of medical records and discussions with the site investigators. The institutional research-ethics board at each institution approved the study. Data on children with sinovenous thrombosis who were enrolled in the registry between January 1, 1992, and December 31, 1997, are included in this report.

In a substudy, performed to assess the completeness of the ascertainment of cases, the Canadian data base for health information was searched for cases of sinovenous thrombosis in children during the study period, with the use of the same ICD-9 codes for sinovenous thrombosis. Cases in Ontario, the province with the largest population, were matched to those in the registry.

From the Divisions of Neurology (G.D.) and Hematology–Oncology (M.A.), the Population Health Sciences Program, Hospital for Sick Children, Toronto; the Department of Pediatrics, University of Toronto, Toronto (G.D., M.A.); the Department of Pediatrics, University of Calgary, Calgary, Alta. (C.A.); the Department of Pediatrics, University of British Columbia, Vancouver (B.B.); the Department of Pediatrics, University of Manitoba, Winnipeg (F.B.); the Department of Pediatrics, Memorial University, St. John's, Nfld. (D.J.B.); the Department of Pediatrics, Dalhousie University, Halifax, N.S. (C.S.C.); the Department of Hematology–Oncology, Université de Montreal, Montreal (M.D.); the Department of Pediatrics, University of Ottawa, Ottawa, Ont. (P.H.); the Department of Pediatric Neurology, Centre Hospitalier de l'Université Laval, Sainte-Foy, Quebec, Que. (P.L.); the Department of Pediatrics, Queen's University, Kingston, Ont. (E.A.M.); and the Departments of Pediatrics and Clinical Neurosciences, University of Western Ontario, London (J.G.) — all in Canada. Address reprint requests to Dr. deVeber at the Division of Neurology, Hospital for Sick Children, 555 University Ave., Toronto, ON M5G 1X8, Canada.

Other authors were Brandon Meaney, M.D. (Department of Pediatrics, McMaster University, Hamilton, Ont.), Michael Shevell, M.D., C.M. (Department of Neurology, Pediatrics, and Neurosurgery, McGill University, Montreal), D. Barry Sinclair, M.D. (Department of Pediatrics, University of Alberta, Edmonton), and Jerome Yager, M.D. (Department of Pediatrics, University of Saskatchewan, Saskatoon).

*Other members of the study group are listed in the Appendix.

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2001 Massachusetts Medical Society. All rights reserved.

Clinical Features

Basic demographic information was recorded, as well as neurologic manifestations of sinovenous thrombosis, which were classified as seizures, diffuse neurologic signs, and focal neurologic signs.

Risk Factors

Findings that were recorded as risk factors included disorders of the head and neck (including local infection), acute systemic illness, chronic systemic disease, and prothrombotic disorders. Standard assays for prothrombotic disorders were used at each center, including activity assays for antithrombin, protein C, protein S, and the lupus anticoagulant; immunologic assays for anticardiolipin antibody; and molecular assays for the presence of factor V Leiden and the G20210A mutation in the prothrombin gene.

Radiologic Evaluation

Sinovenous thrombosis was confirmed by computed tomography (CT), magnetic resonance imaging (MRI) with or without magnetic resonance venography (MRV), conventional angiography, or transfontanel power Doppler ultrasonography. The results of MRI, with the results of MRV when available, were compared with the results of CT or those of power Doppler ultrasonography when both sets of data were available.

The location of the thrombosis was classified as superficial or deep. The presence and nature of parenchymal lesions were noted. Infarcts were classified as nonhemorrhagic or hemorrhagic. Extraparenchymal hemorrhages were classified as subdural, subarachnoid, or intraventricular.

Treatment

The use of antithrombotic agents, other medical therapies, and surgery was recorded. Overt clinical bleeding requiring transfusion therapy, bleeding viewed as excessive and prompting the cessation of anticoagulant therapy, and confirmed bleeding into the central nervous system were considered to be major episodes of bleeding. Recurrent thrombosis was defined as a confirmed thrombotic event within or outside the central nervous system.

Neurologic Outcome

The neurologic outcome, based on the assessment at the last follow-up visit, was classified as normal (no neurologic deficits) or abnormal (one or more neurologic deficits). Neurologic deficits and death due to sinovenous thrombosis were classified as adverse outcomes. Seizures were classified as adverse outcomes only if they occurred after discharge from the acute care hospital and were treated with anticonvulsant agents.

Statistical Analysis

The incidence of sinovenous thrombosis was calculated on the basis of the Canadian population of persons 18 years of age or younger.[12] The following variables were tabulated: patient enrollment in each province, age at the time of presentation, sex, neurologic manifestations, risk factors, radiologic findings, treatment, adverse outcomes, and cause of death.

Statistical analyses were performed with the use of Stat-View 5.1.[13] Univariate analyses were performed with the chi-square test or Fisher's exact test for categorical data and with Student's t-test for continuous data. Potentially important differences between neonates and nonneonates were tested for each of the variables noted above. Univariate analyses were also performed to identify predictors of an adverse outcome; variables included in these analyses were age, sex, presence or absence of seizures, presence or absence of infarcts, location of thrombosis, involvement of single or multiple sinuses, and presence or absence of treatment with antithrombotic agents. Multivariate analyses were planned if more than three variables were found to be significantly associated with an adverse outcome ($P<0.05$) in the univariate analyses.

RESULTS

Patients

A total of 160 consecutive children with sinovenous thrombosis were enrolled in the registry: 69 neonates and 91 nonneonates. The geographic distribution of the patients reflected that of the general population in Canada, with Ontario having the largest number of patients (52 percent). The substudy showed that the registry included 97 percent of the children who were classified as having an ICD-9 code for sinovenous thrombosis in the Ontario health-information data base. The incidence of sinovenous thrombosis was 0.67 case per 100,000 children per year (95 percent confidence interval, 0.55 to 0.76). Information was available for more than 95 percent of the children unless otherwise indicated.

Demographic and Clinical Characteristics

Forty-three percent of the children were neonates, and 54 percent were less than one year old (Fig. 1); 54 percent were male and 46 percent were female. Seizures were more common and both focal and diffuse neurologic signs less common in neonates than in nonneonates (Table 1).

Risk Factors

Risk factors were present in all but four patients (2 percent) and were related to age (Table 2). Acute systemic illnesses were present in 84 percent of neonates; the most frequent illnesses were perinatal complications (in 51 percent) and dehydration (in 30 percent). The perinatal complications included hypoxia at birth (in 30 cases), premature rupture of membranes

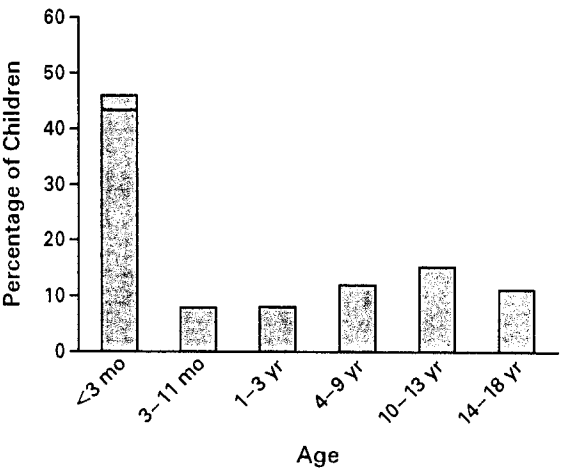

Figure 1. Age Distribution among 160 Children with Sinovenous Thrombosis.

The portion of the first bar below the horizontal line indicates infants less than one month old.

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2001 Massachusetts Medical Society. All rights reserved.

Case 2:08-cv-15075-PDB-SDP ECF No. 1-2, PageID.64 Filed 12/08/08 Page 47 of 51

TABLE 1. NEUROLOGIC MANIFESTATIONS OF SINOVENOUS THROMBOSIS IN 160 CHILDREN.*

NEUROLOGIC MANIFESTATION	TOTAL (N=160)	NEONATES (N=69)	NONNEONATES (N=91)	P VALUE†
	no. of children (%)			
Seizures				
Any	93 (58)	49 (71)	44 (48)	0.006
Generalized	42 (26)	19 (28)	23 (25)	
Not specified	29 (18)	16 (23)	13 (14)	
Focal	27 (17)	17 (25)	10 (11)	
None	63 (39)	17 (25)	46 (51)	
Diffuse neurologic signs				
Any	122 (76)	40 (58)	82 (90)	<0.001
Decreased level of consciousness	70 (44)	25 (36)	45 (49)	
Headache	54 (34)	0	54 (59)	
Jittery movements	27 (17)	14 (20)	13 (14)	
Papilledema	20 (12)	0	20 (22)	
None	34 (21)	26 (38)	8 (9)	
Focal neurologic signs				
Any	68 (42)	20 (29)	48 (53)	0.004
Hemiparesis	21 (13)	4 (6)	17 (19)	
Visual impairment	16 (10)	0	16 (18)	
Cranial-nerve palsies	15 (9)	5 (7)	10 (11)	
Ataxia	6 (4)	0	6 (7)	
Speech impairment	6 (4)	0	6 (7)	
Hemisensory loss	3 (2)	0	3 (3)	
Other	26 (16)	17 (25)	9 (10)	
None	88 (55)	46 (67)	42 (46)	

*Data were available for more than 95 percent of children in all categories. Children may have had more than one neurologic manifestation. All percentages were calculated with a denominator of 160 for the total group, 69 for neonates (<1 month old), and 91 for nonneonates (1 month to 18 years old).

†P values (two-sided) are for comparisons between neonates and nonneonates. Headache, visual impairment, ataxia, speech impairment, and hemisensory loss were excluded from the statistical analysis because they are generally not observed in one of the age groups.

TABLE 2. RISK FACTORS FOR SINOVENOUS THROMBOSIS.*

RISK FACTOR	TOTAL (N=160)	NEONATES (N=69)	NON-NEONATES (N=91)	P VALUE†
	no. of children (%)			
Head and neck disorder	46 (29)	11 (16)	35 (38)	<0.001
Infection	28 (18)	7 (10)	21 (23)	
Other	20 (12)	5 (7)	15 (16)	
Acute systemic illness				
Any	86 (54)	58 (84)	28 (31)	<0.001
Dehydration	40 (25)	21 (30)	19 (21)	
Perinatal complications	38 (24)	35 (51)	3 (3)	
Bacterial sepsis	15 (9)	11 (16)	4 (4)	
None	69 (43)	9 (13)	60 (66)	
Chronic systemic disease				
Any	58 (36)	3 (4)	55 (60)	<0.001
Connective-tissue disease	22 (14)	1 (1)	21 (23)	
Hematologic disorder	20 (12)	2 (3)	18 (20)	
Cancer	12 (8)	0	12 (13)	
Cardiac disease	8 (5)	0	8 (9)	
Disorder requiring indwelling catheter	8 (5)	0	8 (9)	
None	97 (61)	62 (90)	35 (38)	
Prothrombotic state	50 (41)	10 (20)	40 (54)	<0.001
Prothrombotic disorder	39 (32)	10 (20)	29 (39)	
Procoagulant drug	14 (11)	0	14 (19)	
Other	29 (18)	8 (12)	21 (23)	
None	4 (2)	1 (1)	3 (3)	

*For all risk factors except prothrombotic disorders, data were available for more than 95 percent of the children. Children may have had more than one risk factor. The percentages were calculated with a denominator of 160 for the total group, 69 for neonates (<1 month old), and 91 for nonneonates (1 month to 18 years old). Data on prothrombotic disorders were available for 123 of the 160 children (77 percent): 49 neonates and 74 nonneonates.

†P values (two-sided) are for comparisons between neonates and nonneonates. Perinatal complications, connective-tissue disease, and cancer were excluded from the statistical analysis because they are generally not observed in one of the age groups.

(in 4), maternal infection (in 4), placental abruption (in 2), and gestational diabetes (in 2). Head and neck disorders were common in nonneonates (38 percent), and in both neonates and nonneonates, the majority of these disorders (61 percent) were infections. Chronic systemic diseases were also common in nonneonates (present in 60 percent) and were diverse in nature.

Tests for prothrombotic disorders were performed in 123 of the 160 patients (77 percent), of whom 39 (32 percent) had abnormal results. The most frequent abnormality was the presence of anticardiolipin antibody (in 10 children), with IgG titers ranging from 15 to 60 IgG phospholipid units per milliliter. Other abnormalities included decreased levels of protein C (in nine children), antithrombin (in seven), protein S (in five), fibrinogen (in two), and plasminogen (in one) and the presence of a lupus anticoagulant (in four), factor V Leiden (in three), and the G20210A prothrombin-gene mutation (in one). The deficiencies of antithrombin, protein C, and protein S were in many cases caused by an acquired disorder such as liver disease, the nephrotic syndrome, or disseminated intravascular coagulation. Procoagulant drugs were given to 14 children: 11 received asparaginase, and 3 received oral contraceptives.

Radiologic Findings

CT was performed in 153 children (96 percent), MRI with or without MRV in 114 (71 percent), and conventional angiography in 13 (8 percent), with power Doppler ultrasonography in 12 neonates (8 percent). Among the 104 children who underwent CT and MRI, CT did not reveal sinovenous thrombosis in 17 children (16 percent). Power Doppler ultrasonography detected sinovenous thrombosis in 10 of the 12 neonates who underwent both power Doppler ultrasonography and MRI.

Figure 2 shows the structures that were most frequently involved. The location of the thrombosis was superficial in 137 children (86 percent) and deep in 60 (38 percent), with no significant differences between neonates and nonneonates (Table 3). Multiple

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2001 Massachusetts Medical Society. All rights reserved.

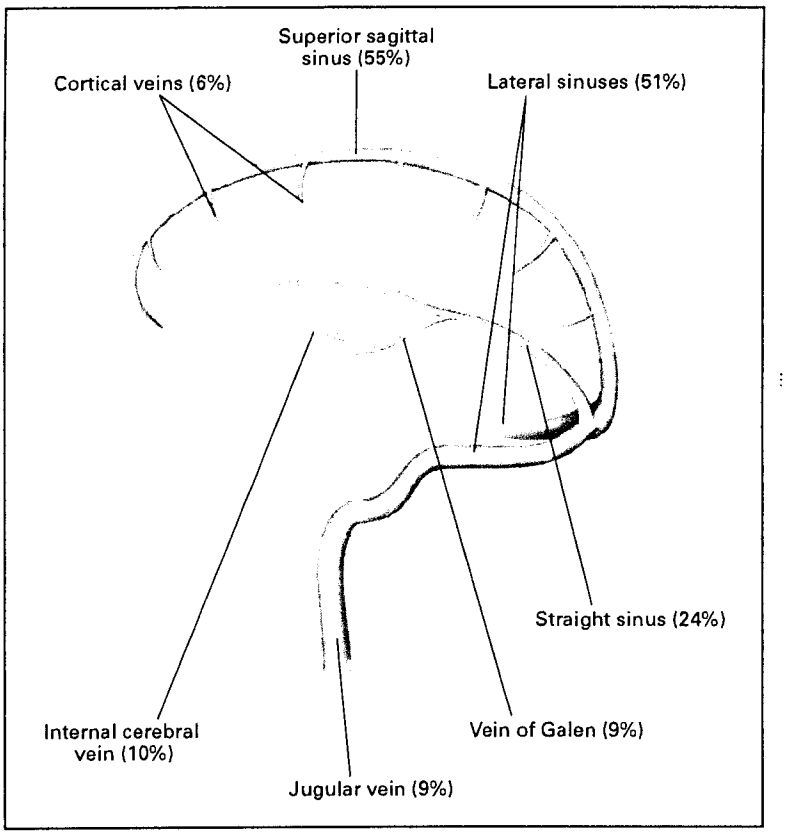

Figure 2. Lateral View of the Cerebral Sinovenous System.
The structures that are most susceptible to sinovenous thrombosis in children are shown, with the relative frequency of involvement given in parentheses. A patient may have multiple sites of involvement.

sinuses were involved in 78 children (49 percent). The lateral sinus was more frequently involved in nonneonates than in neonates (60 percent vs. 39 percent) ($P=0.01$).

Cerebral parenchymal infarcts were present in 66 children (41 percent): 29 neonates and 37 nonneonates. The infarcts were nonhemorrhagic in 21 of the 66 children and hemorrhagic in 45. Twenty-four neonates (35 percent) had hemorrhagic infarcts, as compared with 21 nonneonates (23 percent, $P=0.05$). Parenchymal lesions other than infarcts were present in 11 children; the lesions included brain tumors, arteriovenous malformations, and multifocal white-matter lesions. Extraparenchymal hemorrhage was present in 14 children (9 percent).

Treatment

Antithrombotic therapy was given to 85 children (53 percent): 25 neonates (36 percent) and 60 nonneonates (66 percent) (Table 4). Most children were treated for three months, and none died or had neurologic deterioration because of hemorrhagic complications. Fifty-one neonates (74 percent) required anticonvulsant therapy, as compared with 38 nonneonates (42 percent). Surgical procedures, performed in 21 children (13 percent), consisted of mastoidectomy and shunt placement.

Outcome

The neurologic outcome could be assessed in 143 children (89 percent): 61 of 69 neonates (88 percent) and 82 of 91 nonneonates (90 percent). The mean interval from thrombosis to the last follow-up visit was 1.6 years (range, 0.05 to 5.2). Of these 143 children, 77 (54 percent) were normal, 54 (38 percent) had neurologic deficits, and 12 (8 percent) had died. The neurologic deficits were motor impairment in 80 percent of cases, cognitive impairment in 10 percent, developmental delay in 9 percent, speech impairment in 6 percent, visual impairment in 6 per-

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2001 Massachusetts Medical Society. All rights reserved.

Case 2:08-cv-15075-PDB-SDP ECF No. 1-2, PageID.66 Filed 12/08/08 Page 49 of 51

TABLE 3. LOCATION OF THROMBOSIS.*

LOCATION	TOTAL (N=160)	NEONATES (N=69)	NON-NEONATES (N=91)	P VALUE†
	no. of children (%)			
Superficial	137 (86)	55 (80)	82 (90)	1.03
Superior sagittal sinus	88 (55)	43 (62)	45 (49)	
Lateral sinus	82 (51)	27 (39)	55 (60)	
Cortical vein	10 (6)	2 (3)	8 (9)	
Deep	60 (38)	27 (39)	33 (36)	0.83
Straight sinus	39 (24)	21 (30)	18 (20)	
Internal cerebral vein	16 (10)	7 (10)	9 (10)	
Vein of Galen	14 (9)	8 (12)	6 (7)	
Jugular vein	14 (9)	1 (1)	13 (14)	

*Data were available for more than 95 percent of children in all categories. Children may have had thrombosis in more than one location. All percentages were calculated with a denominator of 160 for the total group, 69 for neonates (<1 month old), and 91 for nonneonates (1 month to 18 years old).

†P values (two-sided) are for comparisons between neonates and nonneonates.

TABLE 4. TYPE OF TREATMENT.*

TREATMENT	TOTAL (N=160)	NEONATES (N=69)	NON-NEONATES (N=91)	P VALUE†
	no. of children (%)			
Antithrombotic therapy	85 (53)	25 (36)	60 (66)	<0.001
Low-molecular-weight heparin	50 (31)	20 (29)	30 (33)	
Unfractionated heparin	35 (22)	6 (9)	29 (32)	
Oral anticoagulant	39 (24)	1 (1)	38 (42)	
Aspirin	9 (6)	0	9 (10)	
Urokinase	1 (1)	0	1 (1)	
Other medical therapy	142 (89)	63 (91)	79 (87)	0.62
Antibiotics	94 (59)	47 (68)	47 (52)	
Anticonvulsants	89 (56)	51 (74)	38 (42)	
Corticosteroids	31 (19)	2 (3)	29 (32)	
Chemotherapy for underlying tumor	7 (4)	0	7 (8)	
Other	31 (19)	10 (14)	21 (23)	
Surgery	21 (13)	3 (4)	18 (20)	0.008

*Data were available for more than 95 percent of children in all categories. Children may have received more than one type of treatment. All percentages were calculated with a denominator of 160 for the total group, 69 for neonates (<1 month old), and 91 for nonneonates (1 month to 18 years old).

†P values (two-sided) are for comparisons between neonates and nonneonates. Chemotherapy was excluded from the statistical analysis because it generally does not apply to neonates.

cent, and other impairments in 26 percent. Of the 12 deaths, 6 were attributable to sinovenous thrombosis and the remainder were attributable to other associated diseases. Predictors of adverse neurologic outcomes included seizures at presentation in nonneonates ($P=0.02$) and the presence of infarcts (nonhemorrhagic or hemorrhagic) in neonates and nonneonates ($P=0.03$). Seizures were present at follow-up in 12 neonates (20 percent) and 9 nonneonates (11 percent, $P=0.22$). Nineteen children (13 percent) had symptomatic recurrent thrombosis: 5 neonates (8 percent) and 14 nonneonates (17 percent, $P=0.19$). Recurrent thrombosis was cerebral in 12 children and noncerebral in 7.

DISCUSSION

The Canadian Pediatric Ischemic Stroke Registry was the source of the data for this large, population-based study of the epidemiology of sinovenous thrombosis during childhood. The incidence of sinovenous thrombosis was 0.67 case per 100,000 children per year, and neonates were the most commonly affected age group. There were age-related differences in the neurologic manifestations of sinovenous thrombosis, and specific risk factors were identified, including head and neck infections and prothrombotic states. Venous infarcts and the occurrence of seizures predicted a poor neurologic outcome.

The registry data pose several methodologic issues that need to be addressed. First, a potential limitation of the data is bias in case ascertainment. Our substudy, however, showed that the registry data accounted for 97 percent of children with sinovenous thrombosis in Ontario, where the majority of the patients lived. Second, the patient cohort was divided into neonates and nonneonates rather than into patients with septic and those with nonseptic sinovenous thrombosis, which is the conventional classification. The validity of the registry classification was supported by the striking differences between the neonatal and nonneonatal groups, and analyses of the registry data according to the presence or absence of sepsis did not reveal any significant differences (data not shown).

Third, testing for prothrombotic disorders was not required, and neither factor V Leiden nor the G20210A mutation in the prothrombin gene had been discovered in the early years of the registry. However, 77 percent of the children were tested, and the results were similar to those in smaller studies in which consecutive children were tested.[14,15] Fourth, one of the limitations of any registry is a lack of standardized data on the long-term outcome. Despite this limitation, data on the neurologic outcome were available for 89 percent of the children in the Canadian registry, and the findings were similar to those in a smaller, hospital-based cohort study.[16]

The main neurologic manifestations of sinovenous thrombosis in the nonneonates in our study were similar to those reported in adults[17]: a decreased level

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2001 Massachusetts Medical Society. All rights reserved.

Case 2:08-cv-15075-PDB-SDP ECF No. 1-2, PageID.67 Filed 12/08/08 Page 50 of 51

of consciousness, headache, focal neurologic signs such as hemiparesis, and cranial-nerve palsies. In contrast, the primary neurologic manifestations in the neonates were seizures and diffuse neurologic signs. The increased frequency of seizures in this group may reflect the general propensity of infants to have seizures. The frequency of seizures and diffuse neurologic signs means that clinicians must have a high index of suspicion for sinovenous thrombosis in neonates.

The risk factors for sinovenous thrombosis in our study were age dependent, were frequently multiple, and were often different from those reported in adults.[17,18] Perinatal complications, of which hypoxic encephalopathy was most common, predominated in the neonates. Head and neck infections, such as otitis media, mastoiditis, and sinusitis, predominated in preschool children, whereas chronic diseases such as connective-tissue disorders were more frequent in older children. Risk factors that are common in adults, such as pregnancy,[19] cancer,[20,21] and use of oral contraceptives,[22] were rare in our study. Idiopathic sinovenous thrombosis represented only 3 percent of cases, as compared with an estimated 10 to 25 percent of cases in adults.[17]

Prothrombotic states may cause or contribute to sinovenous thrombosis in both adults and children. In adults, the frequency of prothrombotic disorders is 15 to 21 percent; the G20210A prothrombin-gene mutation and the presence of factor V Leiden are the most common genetic disorders.[23-25] In children with sinovenous thrombosis, the frequency of prothrombotic disorders is 12 to 50 percent, and the presence of anticardiolipin antibody is the most common acquired disorder.[14,15,26-30] In our study, 32 percent of the children who underwent testing for prothrombotic disorders had at least one abnormality; the presence of anticardiolipin antibody was the most common acquired disorder, and the presence of factor V Leiden was the most common genetic disorder. Other prothrombotic disorders were due to underlying diseases. Whether acquired prothrombotic disorders cause sinovenous thrombosis in children or are merely associated with it remains to be determined.

The registry offered a unique opportunity to compare the accuracy of the various radiographic tests used to diagnose sinovenous thrombosis in children. Although CT scans were obtained in 96 percent of the children, they detected the disorder in only 84 percent of the children who also underwent MRI with MRV. Previous studies have suggested that CT scans may also have false positive results in neonates because of an increased hematocrit, a decreased density of unmyelinated white matter, and slower venous flow — factors that may result in radiographic findings that mimic the dense-triangle sign.[31] Transfontanel power Doppler ultrasonography is a powerful tool for the noninvasive diagnosis and monitoring of neonatal sinovenous thrombosis.[32] At this time, the optimal technique for establishing the diagnosis in children is MRI with MRV.

The use of anticoagulant therapy in adults with sinovenous thrombosis is based on data from four clinical trials that showed an improved neurologic outcome with this treatment.[33-36] The extrapolation of these results to children with sinovenous thrombosis, particularly neonates, is problematic, because the ratio of efficacy to safety may differ from that in adults. The registry data show that anticoagulants are frequently used in children with sinovenous thrombosis, especially in nonneonates (66 percent). Although the potential benefit of anticoagulants in children with sinovenous thrombosis cannot be determined from the registry data, the results of our study suggest that anticoagulant therapy is not associated with serious hemorrhage in selected patients and that such therapy warrants further evaluation, particularly in neonates.

The long-term neurologic outcome of sinovenous thrombosis in children is unclear.[9,10] The best available estimate is that after a mean of 2.1 years, 77 percent of neonates and 52 percent of nonneonates are neurologically normal.[16] Our findings are consistent with those estimates. Long-term follow-up of affected children is very important, especially in neonates, since the onset of signs of neurologic injury is delayed in this age group. Given the increasing incidence of sinovenous thrombosis in children, the variations in treatment, and the adverse outcomes in half the children with this disorder, studies are needed to identify more effective immediate and secondary preventive therapies.

Supported by grants from the Heart and Stroke Foundation of Ontario (NA4107) and the Bloorview Children's Hospital Foundation. Dr. deVeber is the recipient of a Stroke Investigator Award from the Heart and Stroke Foundation of Ontario. Dr. Andrew is the recipient of a Career Scientist Award from the Heart and Stroke Foundation of Canada.

The following investigators also participated in the study: **Canada** — *Alberta:* S. Lee, B. Prieur; *British Columbia:* S. Kent, J.A.R. Tibbles; *Manitoba:* P.J. McCusker; *Newfoundland:* S. Penney; *New Brunswick:* D.C. Meek; *Nova Scotia:* E. Woods; *Ontario:* M. Adams, A.K.C. Chan, S.N. Christie, R.M. Curtis, T. Domi, M.P. Flavin, L.F. Jardine, J.A. Julian, D.L. Keene, S. Lanthier, D.L. MacGregor, S. Mayank, L. Mitchell, J. Tu, L. Wylie; *Quebec:* B.G. Lemieux; **Australia** — P. Monagle.

REFERENCES

1. Medlock MD, Olivero WC, Hanigan WC, Wright RM, Winek SJ. Children with cerebral venous thrombosis diagnosed with magnetic resonance imaging and magnetic resonance angiography. Neurosurgery 1992;31:870-6.
2. Yuh WT, Simonson TM, Wang AM, et al. Venous sinus occlusive disease: MR findings. AJNR Am J Neuroradiol 1994;15:309-16.
3. Casey SO, Alberico RA, Patel M, et al. Cerebral CT venography. Radiology 1996;198:163-70.
4. Scotti LN, Goldman RL, Hardman DR, Heinz ER. Venous thrombosis in infants and children. Radiology 1974;112:393-9.
5. Rao KC, Knipp HC, Wagner EJ. Computed tomographic findings in cerebral sinus and venous thrombosis. Radiology 1981;140:391-8.
6. Lee BC, Voorhies TM, Ehrlich ME, Lipper E, Auld PA, Vannucci RC. Digital intravenous cerebral angiography in neonates. AJNR Am J Neuroradiol 1984;5:281-6.
7. Justich E, Lammer J, Fritsch G, Beitzke A, Walter GF. CT diagnosis of thrombosis of dural sinuses in childhood. Eur J Radiol 1984;4:294-5.

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2001 Massachusetts Medical Society. All rights reserved.

8. Baram TZ, Butler IJ, Nelson MD Jr, McArdle CB. Transverse sinus thrombosis in newborns: clinical and magnetic resonance imaging findings. Ann Neurol 1988;24:792-4.
9. Shevell MI, Silver K, O'Gorman AM, Watters GV, Montes JL. Neonatal dural sinus thrombosis. Pediatr Neurol 1989;5:161-5.
10. Barron TF, Gusnard DA, Zimmerman RA, Clancy RR. Cerebral venous thrombosis in neonates and children. Pediatr Neurol 1992;8:112-6.
11. International classification of diseases, 9th rev., clinical modification: ICD-9-CM. 5th ed. 1997 Hospital ed. Los Angeles: Practice Management Information, 1996.
12. Statistics Canada. CANSIM. (Accessed July 18, 2001, at http://www.statcan.ca/english/Pgdb/People/Population/demo10a.htm.)
13. Stat-view, version 5.1. Cary, N.C.: SAS Institute, 1998 (software).
14. deVeber G, Monagle P, Chan A, et al. Prothrombotic disorders in infants and children with cerebral thromboembolism. Arch Neurol 1998;55:1539-43.
15. Bonduel M, Sciuccati G, Hepner M, Torres AF, Pieroni G, Frontroth JP. Prethrombotic disorders in children with arterial ischemic stroke and sinovenous thrombosis. Arch Neurol 1999;56:967-71.
16. deVeber GA, MacGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. J Child Neurol 2000;15:316-24.
17. Bousser M-G, Russell RR. Cerebral venous thrombosis. Vol. 33 of Major problems in neurology. London: W.B. Saunders, 1997.
18. Einhäupl KM, Villringer A, Haberl RL, et al. Clinical spectrum of sinus venous thrombosis. In: Einhäupl K, Kempski O, Baethmann A, eds. Cerebral sinus thrombosis: experimental and clinical aspects. New York: Plenum Press, 1990:149-55.
19. Cantu C, Barinagarrementeria F. Cerebral venous thrombosis associated with pregnancy and puerperium: review of 67 cases. Stroke 1993;24:1880-4.
20. Hickey WF, Garnick MB, Henderson IC, Dawson DM. Primary cerebral venous thrombosis in patients with cancer — a rarely diagnosed paraneoplastic syndrome: report of three cases and review of the literature. Am J Med 1982;73:740-50.
21. Brown MT, Friedman HS, Oakes WJ, Boyko OB, Schold SC Jr. Sagittal sinus thrombosis and leptomeningeal medulloblastoma. Neurology 1991;41:455-6.
22. Dindar F, Platts ME. Intracranial venous thrombosis complicating oral contraception. Can Med Assoc J 1974;111:545-8.
23. Deschiens MA, Conard J, Horellou MH, et al. Coagulation studies, factor V Leiden, and anticardiolipin antibodies in 40 cases of cerebral venous thrombosis. Stroke 1996;27:1724-30.
24. Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci PM. High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. N Engl J Med 1998;338:1793-7.
25. Zuber M, Toulon P, Marnet L, Mas JL. Factor V Leiden mutation in cerebral venous thrombosis. Stroke 1996;27:1721-3.
26. Prats J, Garaizar C, Zuazo E, Lopez J, Pinan MA, Aragues P. Superior sagittal sinus thrombosis in a child with protein S deficiency. Neurology 1992;42:2303-5.
27. Rich C, Gill JC, Wernick S, Konkol RJ. An unusual cause of cerebral venous thrombosis in a four-year-old child. Stroke 1993;24:603-5.
28. van Kuijck MA, Rotteveel JJ, van Oostrom CG, Novakova I. Neurological complications in children with protein C deficiency. Neuropediatrics 1994;25:16-9.
29. Uziel Y, Laxer RM, Blaser S, Andrew M, Schneider R, Silverman ED. Cerebral vein thrombosis in childhood systemic lupus erythematosus. J Pediatr 1995;126:722-7.
30. von Scheven E, Athreya BH, Rose CD, Goldsmith DP, Morton L. Clinical characteristics of antiphospholipid antibody syndrome in children. J Pediatr 1996;129:339-45.
31. Ludwig B, Brand M, Brockerhoff P. Postpartum CT examination of the heads of full term infants. Neuroradiology 1980;20:145-54.
32. Bezinque SL, Slovis TL, Touchette AS, et al. Characterization of superior sagittal sinus blood flow velocity using color flow Doppler in neonates and infants. Pediatr Radiol 1995;25:175-9.
33. Einhaupl KM, Villringer A, Meister W, et al. Heparin treatment in sinus venous thrombosis. Lancet 1991;338:597-600.
34. Maiti B, Chakrabarti I. Study on cerebral venous thrombosis with special reference to efficacy of heparin. J Neurol Sci 1997;150:Suppl:S147. abstract.
35. Nagaraja D, Haridas T, Taly AB, Veerendrakumar M, SubbuKrishna DK. Puerperal cerebral venous thrombosis: therapeutic benefit of low dose heparin. Neurol India 1999;47:43-6.
36. de Bruijn SF, Stam J. Randomized, placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis. Stroke 1999;30:484-8.

Copyright © 2001 Massachusetts Medical Society.

POSTING PRESENTATIONS AT MEDICAL MEETINGS ON THE INTERNET

Posting an audio recording of an oral presentation at a medical meeting on the Internet, with selected slides from the presentation, will not be considered prior publication. This will allow students and physicians who are unable to attend the meeting to hear the presentation and view the slides. If there are any questions about this policy, authors should feel free to call the *Journal*'s Editorial Offices.

Downloaded from www.nejm.org at Eli Lilly on August 30, 2008 .
Copyright © 2001 Massachusetts Medical Society. All rights reserved.